

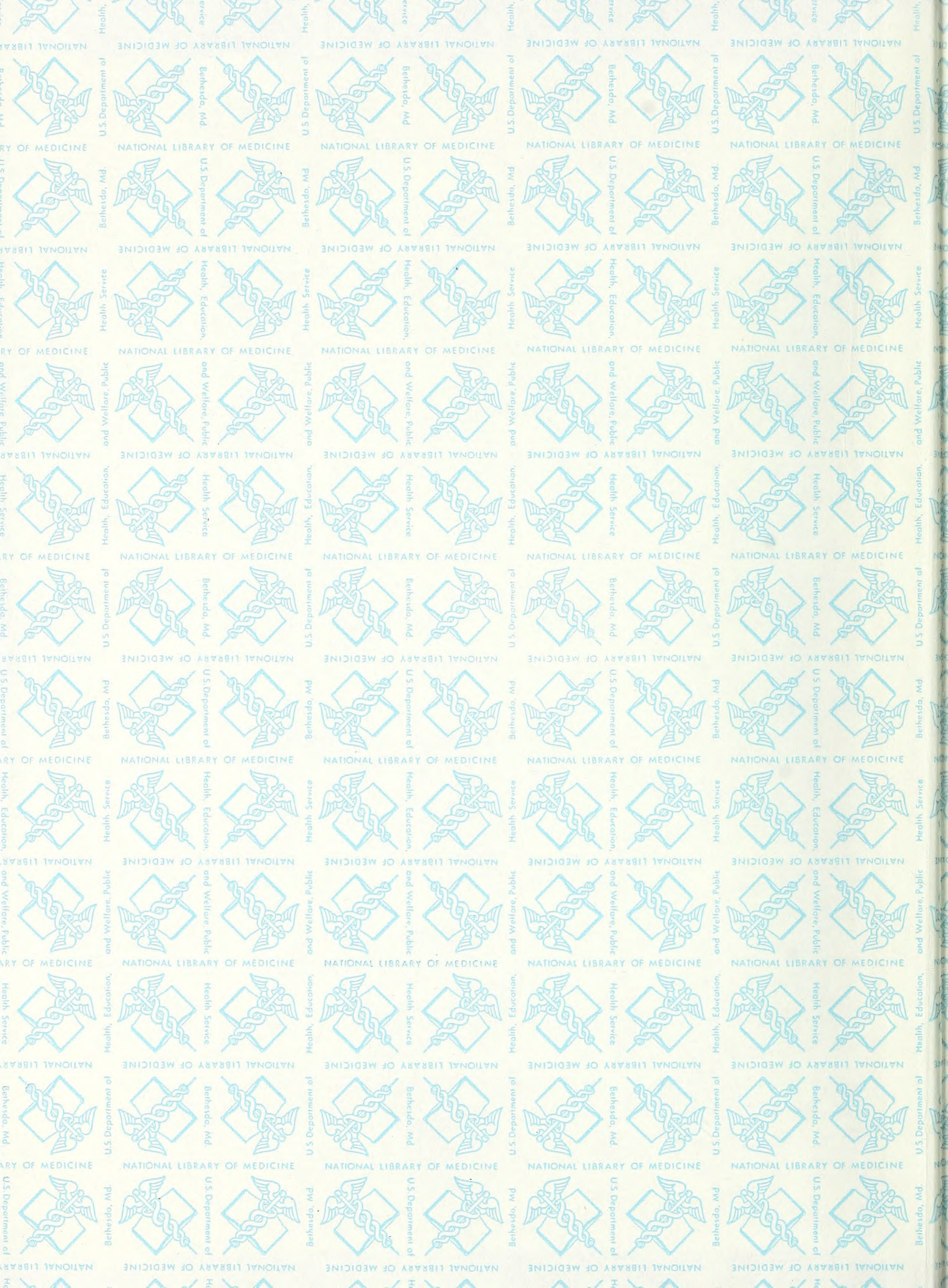
**SPEECHES, ARTICLES, AND  
SELECTED PAPERS**

**Donald S. Fredrickson, M. D.**

**1975-1981**

**Volume 2**















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Speeches, Articles, and Selected Papers

Donald S. Fredrickson, M.D.

1977-1978

Volume 2

CONTENTS

<u>Date</u>	<u>Place</u>	<u>Title and Audience</u>	<u>Page</u>
Jan./Feb. 1977	National Institutes of Health (U.S.)		
	Office of the Director		
Feb. 14, 1977	NIH Bethesda, Md.	History of the NIH	408
Feb. 19, 1977	NIH Bethesda, Md.	Opening remarks at reception By Donald S. Fredrickson, M.D.	
		1975-1981	
Mar. 4, 1977	U.S. House of Representatives, Wash., D.C.	Statement before Subcommittees on Labor, Health, Education, and Welfare; Committee on Appropriations, FY 1978 Appropriations	41
		Volume 2 (of 3) (1977-1978)	
Mar. 9, 1977	Wash., D.C.	"An Overview of the Role of NIH and Other Federal Agencies in the Conduct of Research with Recombinant DNA," National Academy of Sciences	42
Mar. 10, 1977	U.S. House of Representatives, Wash., D.C.	Statement before Subcommittee on the Environment and the Atmosphere, Committee on Science and Technology, Environmental Health Research at the NIH	43
Mar. 15, 1977	U.S. Senate Wash., D.C.	Statement before Subcommittee on Labor, Health, Education, and Welfare; Committee on Appropriations, FY 1978 Appropriations	44
Mar. 17, 1977	U.S. House of Representatives, Wash., D.C.	Statement before Subcommittee on Health and the Environment, Committee on Labor and Human Resources, Senate	45



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1975-81

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National Archives and Records Administration  
Office of the Director

SPEECHES, ARTICLES, AND SELECTED PAPERS

By

Donald S. Fredrickson, M.D.

1975-1981

Volume 2 (of 3)  
(1977-1978)



<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
Mar. 31, 1977		<u>Speeches, Articles, and Selected Papers</u> <u>Donald S. Fredrickson, M.D.</u> 1977-1978 Volume 2	

# CONTENTS

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
Jan./Feb. 1977	-	"Cancer--The Outlaw Cell," article from <u>Chemistry</u> . . . . .	.40A
Feb. 14, 1977	NIH Bethesda, Md.	Introductory remarks for Mr. Carl Rowan, National Black History Observance. . . . .	.40B
Feb. 19, 1977	NIH Bethesda, Md.	Opening remarks at recom- binant DNA meeting with dis- tinguished scientists and academicians. . . . .	.41
Mar. 4, 1977	U.S. House of Representatives, Wash., D.C.	Statement before Subcom- mittee on Labor-Health, Education, and Welfare; Committee on Appropriations. FY 1978 Appropriations. . . . .	.42
Mar. 9, 1977	Wash., D.C.	"An Overview of the Role of NIH and Other Federal Agencies in the Conduct of Research With Re- combinant DNA," National Academy of Sciences . . . . .	.43
Mar. 10, 1977	U.S. House of Representatives, Wash., D.C.	Statement before Subcommittee on the Environment and the Atmos- phere, Committee on Science and Technology; Environmental Health Research at the NIH . . . . .	.44
Mar. 15, 1977	U.S. Senate Wash., D.C.	Statement before Subcommittee on Labor, Health, Education, and Welfare; Committee on Appropri- ations. FY 1978 Appropriations . . . . .	.45
Mar. 17, 1977	U.S. House of Representatives, Wash., D.C.	Statement before Subcommittee on Health and the Environment, Com- mittee on Interstate and Foreign Commerce; Recombinant DNA Research. . . . .	.46







Speeches, Articles, and Selected Papers; Donald S. Fredrickson, M.D.,  
Vol. 2 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
Mar. 31, 1977	U.S. House of Representatives, Wash., D.C.	Statement before Subcommittee on Science, Research and Technology; Committee on Science and Technology. Science Policy Implications of DNA Recombinant Molecule Research. . . .	.47
April 1977	- U.S. Senate Wash., D.C.	"Fredrickson on the NIH Future," interview published in the <u>Blue Sheet</u> . . . . .	.48
Apr. 4, 1977	Chicago, Ill.	"Research and the Political Process," Federation of American Societies for Experimental Biology. . . . .	.49
Apr. 6, 1977	U.S. Senate, Wash., D.C.	Statement before Subcommittee on Health and Scientific Research, Committee on Human Resources; Recombinant DNA Regulation Act, 1977 . . . . .	.50
Apr. 12, 1977	New Orleans, La.	"Recumbent DNA: Our Latent Dowries of Native Ability," Xavier University-MBS Biomedical Symposium . . . . .	.51
Apr. 18, 1977	NIH Bethesda, Md.	Welcoming remarks, Conference on Environmental Health and Safety Requirements for Sponsored Research in Higher Education. . . . .	.52
Apr. 26, 1977	Georgetown Univ., Wash., D.C.	Welcoming remarks for Dr. H. Tristram Engelhardt, Jr., Rosemary Kennedy Professorship . . . .	.53
May 2, 1977	Wash., D.C.	"Aesculapian Merry-Go-Round," Assoc. of American Physicians. . . .	.54
May 20, 1977	Nutley, N.J.	"Research, the Public and the Private," Roche Institute of Molecular Biology. . . . .	.55
May 31, 1977	Stockholm, Sweden	Remarks presented upon receiving an honorary degree in medicine from Karolinska Institutet . . . . .	.56







Speeches, Articles, and Selected Papers; Donald S. Fredrickson, M.D.,  
Vol. 2 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
June 7, 1977	U.S. Senate, Wash., D.C.	Statement before Subcommittee on Health and Scientific Research, Committee on Human Resources; The Banning of Saccharin, 1977. . . . .	.57
June 10, 1977	U.S. Senate Wash., D.C.	Statement before Subcommittee on Health and Scientific Re- search, Committee on Human Resources; Environmental Health Science . . . . .	.58
June 17, 1977	Wash., D.C.	Talk presented at Claude Bernard Science Journalism Awards Luncheon, National Society for Medical Research . . . . .	.59
June 26, 1977	Philadelphia, Pa.	"Medicine, Science, and Society," Vith International Congress on Thrombosis and Haemostasis. . . . .	.60
June 27, 1977	NIH Bethesda, Md.	Welcoming remarks, Ninth Annual Honor Award Ceremony . . . . .	.61
July 12, 1977	U.S. Senate Wash., D.C.	Statement before Subcommittee on Health and Scientific Re- search, Committee on Human Resources; Banning of the Drug Laetrile from Interstate Commerce by FDA. . . . .	.62
Aug. 2, 1977	U.S. House of Representatives, Wash., D.C.	Statement before Subcommittee on Domestic and International Scientific Planning, Analysis and Cooperation; Committee on Science and Technology. Nutri- tion-Related Oversight Review. . . . .	.63
Sept. 12, 1977	NIH Bethesda, Md.	Remarks presented at National Hispanic Heritage Observance . . . . .	.64
Sept. 14, 1977	NIH Bethesda, Md.	Opening remarks presented at NIH/NCI Consensus Development on Breast Cancer Screening . . . . . and article on "Seeking Tech- nical Consensus on Medical Interventions" . . . . .	.65 .66







Speeches, Articles, and Selected Papers; Donald S. Fredrickson, M.D.,  
Vol. 2 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
Sept. 15, 1977	NIH Bethesda, Md.	Opening remarks presented at 1977 NIH Asian-American Cultural Celebration. . . . .	.67
Sept. 16, 1977	U.S. Senate Wash., D.C.	Statement before Subcommittee on Health and Scientific Research, Committee on Human Resources; Biomedical Research Related to Prevention of Disease. . . . .	.68
Sept. 19, 1977	Bethesda, Md.	Remarks presented at DRR's 15th Anniversary. . . . .	.69
Oct. 3, 1977	NIH Bethesda, Md.	Welcoming remarks presented at National Conference on Clinical Trial Methodology. . . . .	.70
Oct. 6, 1977	U.S. House of Representatives, Wash., D.C.	Statement before Subcommittee on Domestic Marketing, Consumer Relations, and Nutrition; Com- mittee on Agriculture. Nutrition Education. . . . .	.71
Oct. 12, 1977	Rochester, N.Y.	"Wilson Day Address," University of Rochester School of Medicine and Dentistry. . . . .	.72
Oct. 17, 1977	U.S. Senate Wash., D.C.	Statement before Select Committee on Nutrition and Human Needs; Diet Related to Killer Diseases, VIII . . . . .	.73
Oct. 25, 1977	Wash., D.C.	"Health Science: Status Report," Institute of Medicine, National Academy of Sciences. . . . .	.74
Oct. 27, 1977	NLM, NIH Bethesda, Md.	Opening remarks presented to Inter- national MEDLARS Policy Advisory Group. . . . .	.75
Nov. 2, 1977	NIH Bethesda, Md.	Introductory remarks for Dr. Philip Leder, Mider Lecture . . . . .	.76
Nov. 8, 1977	U.S. Senate Wash., D.C.	Statement before Subcommittee on Science, Technology, and Space; Committee on Commerce, Science, and Transportation. Recombinant DNA. . . . .	.77







Speeches, Articles, and Selected Papers; Donald S. Fredrickson, M.D.,  
Vol. 2 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
Nov. 10, 1977	NIH Bethesda, Md.	Welcoming remarks presented at swearing-in ceremonies for Dr. Upton, appointed Director of NCI. . . . .	.78
Dec. 7, 1977	NIH Bethesda, Md.	Opening remarks presented at public meeting on genetics, sponsored by Public Health Service Genetics Coordinating Committee. . . . .	.79
Dec. 8, 1977	Wash., D.C.	"The State of Nutrition Re- search," Food and Nutrition Board, National Academy of Sciences . . . . .	.80
Dec. 15, 1977	NIH Bethesda, Md.	Opening remarks presented at Director's Advisory Committee meeting on proposed revision of NIH Guidelines on recom- binant DNA research. . . . .	.81
Feb. 8, 1978	U.S. Senate Wash., D.C.	Statement before Subcommittee on Health and Scientific Re- search, Committee on Human Resources; Biomedical Research Extension Acts of 1978 . . . . .	.82
Feb. 8, 1978	Wash., D.C.	"Role of the Federal Government," 30th Anniversary of NHLBI. . . . .	.83
Feb. 13, 1978	NIH Bethesda, Md.	Opening remarks presented during Black History Week Observance. . . . .	.84
Feb. 22, 1978	U.S. Senate Wash., D.C.	Statement before Subcommittee on Labor, Health, Education, and Welfare; Committee on Appropri- ations. FY 1979 Appropriations. . . . .	.85
Mar. 2, 1978	U.S. House of Representatives Wash., D.C.	Statement before Subcommittee on Labor-Health, Education, and Welfare; Committee on Appro- priations. FY 1979 Appropriations . . . . .	.86
Mar. 29, 1978	NIH Bethesda, Md.	Introductory remarks for Dr. Eric Kandel, NIH lecture. . . . .	.87
Apr. 9, 1978	Wash., D.C.	Remarks presented to National Science Teachers Association . . . . .	.88







Speeches, Articles, and Selected Papers; Donald S. Fredrickson, M.D.,  
Vol. 2 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
Apr. 10, 1978	Atlantic City, N.J.	"The Administration's View of Basic Research and the Life Sciences," Federation of Amer- ican Societies for Experimental Biology. . . . .	.89
Apr. 11, 1978	U.S. House of Representatives Wash., D.C.	Statement before Subcommit- tee on Science, Research and Technology; Committee on Science and Technology; Recombinant DNA Act. . . . .	.90
Apr. 27, 1978	NIH Bethesda, Md.	Opening remarks presented to Recombinant Molecule Program Advisory Committee . . . . .	.91
May 10, 1978	NIH Bethesda, Md.	Introductory remarks for Dr. Har Gobind Khorana, Alfred P. Sloan Professor of Biology and Chemistry at MIT . . . . .	.92
May 11, 1978	NIH Bethesda, Md.	Remarks presented at 1978 NIH Asian-American Cultural Pro- gram . . . . .	.93
May 31, 1978	NIH Bethesda, Md.	Introductory remarks for Dr. Robert M. Chanock, Dyer Lec- ture . . . . .	.94
June 1, 1978	N.Y., N.Y.	"Federalism in Science: How Much is Enough?" Mt. Sinai Alumni Day . . . . .	.95
June 13, 1978	U.S. Senate Wash., D.C.	Statement before Subcommit- tee on Nutrition, Committee on Agriculture, Nutrition, and Forestry; Nutrition Research . . . . .	.96
June 19, 1978	NIH Bethesda, Md.	Opening remarks presented at Nutrition Conference on Bio- medical and Behavioral Basis of Clinical Nutrition: A Pro- jection for the 1980s. . . . .	.97
June 19, 1978	Wash., D.C.	Transcript of "War on Cancer," MacNeil/Lehrer Report with Senator Dole . . . . .	.98





Speeches, Articles, and Selected Papers; Donald S. Fredrickson, M.D.,  
Vol. 2 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
June 26, 1978	U.S. Senate Wash., D.C.	Statement before Subcommittee on Monopoly and Anticompeti- tive Activities, Select Com- mittee on Small Business. Government Patent Policies: Institutional Patent Agree- ments. . . . .	99
June 29, 1978	U.S. House of Representatives Wash., D.C.	Statement before Subcommittee on Health and the Environment, Committee on Interstate and Foreign Commerce; Research Needs in Nephrology and Urology. . . . .	100
July 28, 1978	-	Decision of the Director, NIH, To Issue Revised Guidelines for Recombinant DNA Research, <u>Fed</u> <u>Reg</u> 43:33043-33069 . . . . .	101 ✓
Aug. 22, 1978	Stockholm, Sweden	"A Scientist's View of Prior- ities and Control in the Organization of Research," Nobel Symposium on Ethics for Science Policy . . . . .	102 ✗
Sept. 10, 1978	Atlanta, Ga.	Remarks presented at More- house College Convocation. . . . .	103
Sept. 14, 1978	NIH Bethesda, Md.	Remarks presented at Hispanic Cultural Ceremonies. . . . .	104
Sept. 17, 1978	Wash., D.C.	"Health Science: The Promise and the Problems," Second World Congress of Nuclear Medicine and Biology . . . . .	105
Sept. 18, 1978	NIH Bethesda, Md.	Remarks presented at ribbon cutting ceremony to open first parking area of Ambulatory Care Research Facility . . . . .	106
Sept. 24-30, 1978	Rome and London	"Recombinant Odyssey II," notes on visit . . . . .	107
Oct. 3, 1978	NIH Bethesda, Md.	"Conference Chairman's Over- view Statement," National Conference on Health Research Principles . . . . .	108





Speeches, Articles, and Selected Papers; Donald S. Fredrickson, M.D.,  
Vol. 2 (Cont.)

<u>Date</u>	<u>Place</u>	<u>Title and audience</u>	<u>Doc.</u>
Oct. 4, 1978	NIH Bethesda, Md.	Closing remarks presented at National Conference on Health Research Principles. . . . .	109
Oct. 10, 1978	Washington Univ., St. Louis, Mo.	"Minding the Biomedical Con- tinuum," Wendell G. Scott Lecture. . . . .	110
Oct. 18, 1978	NIH Bethesda, Md.	Introductory remarks for Dr. Frank H. Ruddle, Dyer Lecture. . . .	111
Nov. 4, 1978	Toronto Canada	Remarks presented upon receiving Gairdner Award, Gairdner Fnd . . . .	112A
Dec. 1978	-	"The National Institutes of Health, Yesterday, Today, and Tomorrow," article from <u>Public Health Reports</u> . . . . .	112B
Dec. 22, 1978	-	NIH Recombinant DNA Research Revised Guidelines, <u>Fed Reg</u> 43: 60080-60105. . . . .	113 ✓





# Cancer— The Outlaw Cell

**Donald S. Fredrickson**

Director, National Institutes of Health, Bethesda, MD 20014

In this and succeeding issues of *Chemistry*, leading scientists discuss the state of the art in cancer research—the search for the causes of cancer, the properties that distinguish cancerous from normal cells, and the approaches to treatment and potential cure.

Cancer, a group of more than 100 different diseases that strike people of all races and ages, is certainly a major national health problem. Some believe it to be the main problem. In 1976 approximately 650 000 Americans were discovered to have cancer, and more than 1 million were treated for the disease. About 370 000 died, a toll greater than the combat deaths in Vietnam and Korea combined.

Cancer is costly. Hospitalization costs for 1976 are estimated at more than \$1.5 billion. If loss of productivity and earning power is added, the economic loss soars to \$15 to \$25 billion annually. Three types of agents are known to cause cancer in laboratory animals: viruses, ionizing and ultraviolet radiation, and chemicals. All three are known to react with the hereditary substance, DNA, in the nucleus of the cell. How these reactions cause cancer remains an area of speculation and active investigation.

Many scientists believe that most cancers are associated in some way with smoking, diet, sunlight, and other environmental factors in the home or workplace. This means that many cancers, perhaps most of them, ultimately can be prevented. Chemicals such as the polycyclic aromatic hydrocarbons in cigarettes, vinyl chloride and asbestos in industry, pesticides and synthetic additives in foods, and chlorinated hydrocarbons in drinking water are a few examples of suspected environmental carcinogens.

The National Cancer Institute is currently testing chemicals using laboratory animals, mainly mice, rats, and hamsters to help identify chemicals in the environment which may cause cancer in man. At the same time, epidemiologists are looking for clues to specific cancer-causing agents by studying the occurrence of cancer in population groups.

As cells are transformed from normal to cancerous in laboratory studies, they acquire unique surface properties or alterations in membrane chemistry. Such alterations are thought to allow the cells to proliferate free from the controls placed on normal cells by the body. Metastases, the spread of cancer cells from the original



tumor, are thought to result from these special changes and from new chemical messages that are released by the changed cells, such as those which enable tumors to develop blood vessels.

One such surface change has led to a whole new area of cancer research—tumor immunology. Studies of cancer cells revealed that they have unique antigens that are recognized as foreign by the immune system, the body's defense mechanism. Under some conditions, the white blood cells and antibodies of the immune system respond to these foreign antigens and destroy the cancer cell.

One popular theory holds that cancer develops when its cells overwhelm the immune system. This theory is based in part on observations of cancer in people with deficient immune systems. Kidney transplant recipients, for example, who are given immunosuppressive drugs to prevent graft rejection, have a risk of developing certain cancers 35 times greater than that of people in the general population.

The newest method of cancer treatment is rooted in the immune concept. Immunotherapy attempts to stimulate the cancer patient's immune system to attack his own cancer cells. Investigators are trying a variety of approaches, including purified tumor antigens, substances isolated from active white blood cells, and chemicals and bacteria that produce a general immune stimulation. At present, immunotherapy is used together with established methods of cancer treatment—surgery, chemotherapy, and radiation.

Although radiation and chemicals can cause cancer, they are used also for treating cancer, and probably act by attacking the DNA of the cancer cell. Radiation therapy utilizing x-rays, radioactive chemicals, and more recently neutrons and pions, is directed at cancer cells within the area of the original tumor.



*DONALD S. FREDRICKSON, director of the National Institutes of Health, is highly regarded in the scientific world for his research in cardiovascular disease. He is a member of many medical societies both domestic and foreign, and headed the delegation representing American Scientists of the American-Soviet cooperative health program in cardiovascular diseases. In 1974 Dr. Fredrickson became president of the Institute of Medicine of the National Academy of Sciences.*

Treatment with chemicals is directed at cancer cells that have metastasized to distant parts of the body and also the primary tumor. This is a fairly new field that grew out of World War II medical research with the mustard gases; now over 50 active anticancer drugs are available. At present, chemotherapy is used mainly in combination with surgery and radiation. This approach is beginning to look promising for cancers of the breast, colon and rectum, and lung.

We still have an enormous amount to learn about cancer, both at the cellular level and as a human problem of prevention and treatment. To enhance research and stimulate the use of new knowledge in medical practice, Congress passed the National Cancer Act in 1971. The Act charged the National Cancer Institute with planning, developing, and coordinating an overall national strategy against cancer. In general terms this strategy for research and demonstration seeks to develop the means to prevent cancer, to cure it when it cannot be prevented, and to achieve long-term survival when it cannot be cured. Rehabilitation programs to improve quality of life are included in this effort.

Though we still do not understand fully the basic mechanisms of cancer, much progress has been made, particularly in the diagnosis and treatment. Acute leukemia in children, Hodgkin's disease, and other lymphomas and choriocarcinoma in women are now curable in a good percentage of patients through the use of combination chemotherapy. Biochemical markers, substances in blood and urine that correlate with the amount of tumor present, are beginning to provide a valuable aid for both detecting cancer and monitoring the response of patients to treatment.

Clearly, the major challenge in the next 25 years will be prevention of cancer, for here lies the best hope for its control. This means identifying factors that cause or contribute to the development of cancer and modifying their deadly effects if they cannot be eliminated from the environment. Means to assess individual variation in susceptibility must be discovered also.

Chemistry will play a crucial role in meeting this challenge. At present nearly 5000 ongoing cancer research projects in the United States are related to chemistry. This figure probably represents about 75% of all cancer research projects in the world.



NATIONAL BLACK HISTORY MONTH  
NATIONAL INSTITUTES OF HEALTH  
Bethesda, Maryland  
February, 1977

National Institutes of Health theme: BEYOND CIVIL RIGHTS: A  
NEW DAY OF EQUALITY:\*

Black writer Ralph Ellison once called the Black-American an "Invisible Man." For many Americans the realities of Black American life simply do not exist; they are invisible. Instead of knowledge and understanding there are myths of racial inferiority, ignorance, fear, and indifference. The result is an invisible American History, hidden between the lines of most history books, a history of the contributions of Black Americans to American life. Haley's recent book "Roots" and the television series based on it had phenomenal impact because it filled in for many Americans some of the blank pages of our history.

Black Americans helped build this nation. They dreamed its dreams, fought its wars, contributed to its greatness, and more than most Americans, felt the weight of its failure. But their greatest struggle has been against a myth, the myth of racial inferiority. This myth obscures and distorts the image of Black Achievement. Today the myth is dying, centuries of indifference and suppression are beginning to dissolve away, revealing a proud tradition of Black Culture and accomplishments - a living tradition that has remained invisible to many Americans both

\*Hubert H. Humphrey, BEYOND CIVIL RIGHTS: A NEW DAY OF EQUALITY,  
(New York: 1968)

Black and White.

The programs that have been so well planned by our NIH Culture Committee are designed not only to reflect the past, but to better guide us into the future.

Our keynote speaker is no stranger to us.

Carl T. Rowan is read, seen and heard by more Americans than almost any other journalist in the land.

His syndicated column for the Chicago Daily News is carried by newspapers that go into almost half the homes in the United States.

He is a permanent panelist on "Agronsky & Co.," the popular public affairs show which is viewed on television stations in 40 of the nation's largest cities. Mr. Rowan's political and social commentaries are aired regularly on the radio and television stations of Post-Newsweek Broadcasting Company. He is a frequent panelist on "Meet the Press."

He is one of the most sought after lecturers in the United States, delivering at least 40 speeches a year on college campuses and at conventions of teachers, businessmen, civil rights leaders.

Mr. Rowan's broad audiences in every field of journalism result from the fact that no other U.S. journalist can claim his breadth of experience as high-level government official, civic leader, prize-winning foreign correspondent and expert on domestic affairs.



-3-

Carl T. Rowan, 51, was the first Black American to sit with the President's Cabinet and with the U.S. National Security Council. That was in 1964 and 1965 when he was Director of the United States Information Agency in the administration of Lyndon B. Johnson. Earlier, Mr. Rowan had served as John F. Kennedy's ambassador to Finland--at that time the youngest U.S. envoy in the world. Still earlier in the Kennedy administration, he had served as Deputy Assistant Secretary of State for Public Affairs and as a member of the U.S. delegation to the United Nations.

Mr. Rowan has been and is American journalism's loudest, strongest voice in behalf of the nation's poor, its Blacks, its Chicanos and other minorities. It is a pleasure and honor to present Mr. Rowan.

RECOMBINANT DNA MEETING  
with  
DISTINGUISHED SCIENTISTS  
AND ACADEMICIANS

February 19, 1977

Welcome

- Press present, this being an open meeting
- Meeting is not being recorded
- Introductions not necessary

Purpose

The purposes of this meeting are to provide you with certain information, offer opportunity for discussion, and to invite your later reflection upon and dissemination of what is said here to others with similar interests.

The subject is regulation of the use of one set of techniques in scientific research. An intergovernmental committee is engaged in consideration of this subject. It is called the Interagency Committee on Recombinant DNA Research. As its deliberations proceed it is seeking to inform different groups of the general nature of its deliberations and to gain opinions concerning them. Among the groups being informed and consulted by spokesmen for the Committee are, or will be, environmentalists, agricultural researchers, industry, and unions. Many other sectors and the general public will be so informed as the Committee's recommendations are made and passed upward in the Administration and to Congress.



You represent one such group--one having as close an interest in the subject as can be imagined. For, as practicing scientists, representatives of institutions where scientific research is carried out, and others having deep interest in the scientific process, it is your work or discipline which is to be regulated.

In setting a perimeter to the discussion, for which we have relatively so little time, may I state the premise:

It has been agreed that a common standard must everywhere exist for the use of recombinant DNA techniques--until we understand better the potential hazards of such techniques. Some later time in history will be suitable for discussion of the necessity of this agreement or the steps that led to it. It should not be debated again in these few hours allotted us today.

The present fact is that the international scientific community has reached agreement that a common set of standards or principles shall govern use of recombinant DNA techniques--and the question being debated now is how this is to be accomplished.

The nature of society is to attempt to settle a question such as this first along lines of maximum common boundaries of governance or law. For recombinant work, these have so far been national boundaries. The U.S. and the U.K. were first to develop guidelines; Europe, acting initially as individual nations, is beginning to organize a common process; and now Canada has very recently issued a set of guidelines. The substance of all guidelines is sufficiently similar; how to apply them locally and nationally is now the question before everyone.

In the U.S., this question has been accompanied by far more clamor and public attention than in any other country. Some local jurisdictions or states are engaged in numerous actions and debates. The need for Federal action to assure commonality is great. Events are moving more rapidly in this direction than is generally perceived.

It is sometimes maintained that NIH guidelines are voluntary. As all of you know they are not. You are required to implement them. And so are all laboratories using such techniques in research now being conducted by or supported by funds from any Federal agency. All have adopted the NIH guidelines.

So have the member industries of the Pharmaceutical Manufacturers Association--to existing knowledge they are the largest share of American industrial research using such techniques.

Nevertheless, questions exist as to how is compliance with these standards to be monitored and enforced. How is one to ensure that all researchers, within those institutions where the Guidelines are involuntarily required, and all researchers outside those institutions, adhere to them?

For those who believe that the answers to these questions must be found in Federal law, there are two derivative questions:

- 1) Is there existing statutory authority for such regulation?
- 2) If not, what should be the nature of new legislation created for this purpose?

We want to concentrate today upon the answers to these last two questions and upon the immediate and potential consequences those answers will have. First, we believe it desirable to bring you all abreast of certain details relevant to this discussion.



Dr. FREDRICKSON. Mr. Chairman, if you have no objection, I would like to offer my prepared statement for the record and to discuss briefly some major problems, described more extensively there, that relate to some of the major problems common to all the Institutes.

Mr. FLOOD. Suppose you do that.

[Dr. Fredrickson's complete statement follows:]

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE, NATIONAL INSTITUTES  
OF HEALTH, STATEMENT BY THE DIRECTOR, MARCH 4, 1977

Mr. Chairman and members of the committee, as the Directors of each of the 14 components of NIH for which there are separate appropriations will be here to explain their present activities and future plans, I believe that it is appropriate—and, I hope, helpful to the committee—for me to discuss briefly—

Some activities and problems that concern NIH as a whole;

What we are doing in areas in which NIH has new or expanded legislative mandates; and

Areas that I believe need further development.

The major problems that affect the directions in which NIH will move, and the manner in which its programs will develop, during the next few years are common to all, or most, of the Institutes.

The most important of these common problems is the relationship of NIH, as the principal biomedical research agency of the Federal Government, to the health service community—and the extent to which NIH can, or should, take responsibility for activities that lie at the boundary between the conduct of research and the delivery of health services. As clinical research—that is, research involving human patients as distinct from research done solely in the laboratory or with animals—necessarily includes caring for patients, the boundary between research and service is not easy to define. This, of course, complicates any decision on how far NIH should go in carrying out its primary responsibility for the conduct of research.

There can be no doubt that this responsibility includes the communication of research results. Although much of the research supported by NIH, or conducted in its own facilities, is as far removed from the needs at the bedside as exploring for an oilfield is from pumping gasoline into a car, the end product of all the work we do or support is the prevention, cure or amelioration of disease and disability. Due to the complexity of most disease problems, each investigator is, in effect, a subcontractor working on what is often a very small piece of the problem and his results will usually only be of interest and of use to other investigators working on related pieces. But their collective goal is ultimately to put together information that will have a direct bearing on man's ability to prevent or cope with disease. Research, therefore, is not completed until usable results have been made available to health practitioners and to the general public.

We have just prepared a report on the activities initiated by NIH during 1976 for improving the dissemination of research results. I should like to submit a copy for inclusion in the record of these hearings. It is, in both senses, a progress report: first, because we feel that we have, indeed, made some progress in improving communication with health professionals engaged in primary care, and, second, because this is an ongoing and expanding activity for which, we hope, a final report will never be written. In particular, I looked forward to the development of the Lister Hill Center for Biomedical Communications to enhance the ability of NIH to play a more effective role—construction of the long-delayed building for this center is now scheduled to begin in April. The National Library of Medicine, since it became part of NIH, has already moved far beyond the traditional passive archival role of a library and with the completion of the Lister Hill Center its ability to explore and expand innovative technological approaches to the storage, retrieval and dissemination of information will be greatly enhanced. At the same time, I must point out that communication is not a job that NIH can do alone. Our main mission, and our expertise, is in providing the substance of what must be communicated—and here we must constantly strive to do a better job of selecting and displaying what is immediately useful to practitioners and the public. But other agencies, particularly the professional societies and voluntary health groups, are better situated to reach the wide audience to whom communication must be addressed—they must be encouraged

to take a more active part in the bucket brigade carrying knowledge from the research well to the health services.

A more fundamental—and much more complex—problem at the juncture of research and the delivery of health services is how best to transfer the technology developed as the result of research and, more particularly, how to assess or forecast its long-term effects. Many new developments have dangers as well as benefits and they may have economic and social impact as well as purely medical usefulness. Sometimes ethical questions may also arise. In each case, the pluses and minuses must be balanced and the inevitable differences of opinion, even among scientists, must be weighed. To this end, we must seek a technical consensus not merely to determine the clinical significance of new findings but to assess their ethical, social and economic implications. We cannot, in good conscience, widely disseminate research information just because it exists—we must, in so far as is possible, be certain that the full effects, in the broadest sense, of putting it into practice are understood and that it is accompanied by whatever warnings or safeguards are necessary. A fairly lengthy document on the responsibilities of NIH in this connection is being prepared. A draft has been discussed with Director's advisory committee and is now receiving internal review. It will be published shortly and copies will, of course, be sent to this committee.

The best assessment tool for the results of most clinical research is the so-called clinical trial—that is, putting a new procedure into practice under previously agreed and carefully monitored conditions. The Cancer and Heart Institutes have special legislative mandates to conduct such trials but they are, in fact, also conducted under the aegis of each of the other Institutes. In fiscal year 1975, the latest year for which complete figures are available, NIH supported 755 clinical trials at a cost of \$87.8 million. Some of these trials had already been in progress for several years—in fact, \$200 million had been spent on them prior to 1975—and many would continue for several more years at a projected cost of \$345 million. The total cost of these 755 trials will therefore be about \$642 million. The size, complexity and duration of these trials—and, therefore, their individual cost—varies widely. The most expensive were the 26 trials supported by the Heart Institute which will cost an average of a little over \$15 million each. Over half of these 755 trials were supported by the Cancer Institute but they account for only 20 percent (\$132 million) of the projected cost. The average cost of the clinical trials that were active in 1975 will be about \$850,000.

Our involvement in clinical trials has increased during the past 2 years and the future support to which we are now committed is higher than it was in 1975. The time has come to decide how much farther and how rapidly we should go. The first determinant, of course, is what research developments are thought to be ready for clinical trial. This is not always an easy judgment to make and it is here that technical consensus can become particularly important. The public—and, I am sure, the Congress—is anxious that research be brought to its clinical fruition without delay but there can also be real dangers in bringing new techniques into practice too soon. There have been ample tragic warnings that a promising new drug or procedure can do unsuspected harm and it is, I think, abundantly clear that the public interest is best served by prudence and caution. A second factor in planning further trials is, of course, the cost. In this connection, we must consider not only the commitment of future funds for the years it may take to complete the trial but also the difficulty of terminating support when the trial has served its scientific purpose. In too many instances the grant or contract that made the trial possible also had the effect of making possible a service to patients that would, in effect, be terminated when NIH support ceases. With rapidly rising health care cost, ending a trial may raise a serious problem for the institutions in which the trial is being conducted while continuing it would clearly be contrary to the NIH mission and the purpose for which the funds were appropriated. We must, therefore, be careful to enter into costly trials only in circumstances that give assurance that they will produce answers to scientific questions, in a reasonable time, and that the purely service aspect of the clinical work undertaken will be continued under other auspices when the trial has been completed. As research is the primary role of NIH and the principal justification for its budget requests, we must be constantly on guard not to assume—or appear to assume—responsibilities for health care services which we cannot properly undertake.

Among the new and expanded legislative mandates for NIH, the two that have the broadest impact are those for diabetes and arthritis.

The current NIH obligations for diabetes research total \$76 million which is slightly more than the \$73.3 million recommended for fiscal year 1977 by the Diabetes Commission. Of this amount a little over half—\$39.8 million—is in the National Institute of Arthritis, Metabolic and Digestive Diseases which has primary responsibility for diabetes research. But diabetes related research also accounts for \$11.9 million in the Heart Institute; \$9.1 million in the Eye Institute for diabetic retinopathy; \$4.6 million in the Child Health Institutes; \$1.9 million in the Neurology Institute; \$6.4 million in the Division of Research Resources; and lesser amounts, totalling \$2.4 million, in some of the other Institutes. There is, thus, an overall NIH involvement of considerable magnitude and scope in diabetes research. To insure that this broad approach is properly coordinated, I have established an NIH Diabetes Coordinating Committee to complement the activities of the interagency committee and the Diabetes Board already established under Public Law 93-354. A joint advisory group has been set up by the Heart and Arthritis Institutes to assist in arranging a clinical trial on the efficacy of controlling blood glucose in arresting the development of vascular complications of diabetes. The Arthritis Institute is setting up several other advisory groups on various aspects of its diabetes program and is arranging a number of conferences and workshops. Existing advisory groups in other Institutes have also appointed subcommittees or are themselves looking into the diabetic aspects of relevant diseases and conditions. The Institute Directors concerned will testify in more detail on their diabetes related activities.

Research on arthritis is similarly dispersed throughout NIH though in this case the Arthritis Institute continues to carry a larger share of the burden. Our total obligations during fiscal year 1977 will be \$30.5 million of which the Arthritis Institute accounts for \$24.7 million. There are, however, relevant research activities in eight of the other Institutes. We are in the process of reviewing all our arthritis related programs as part of our preparation of the 1979-83 forward plan. When this is completed I shall appoint a coordinating committee similar to the one for diabetes.

The health problems of the aged also cut across the disease-oriented organizational structure of NIH. Dr. Butler—who became the first Director of the National Institute for Aging on May 1, 1976—is therefore much concerned to coordinate the activities of his Institute with the ongoing disease-oriented programs at NIH and with other agencies that have responsibilities and programs affecting the aged. It will be our joint endeavor to insure that, on the one hand, there is no unnecessary overlap or duplication and, on the other hand, that there is optimal cooperation and collaboration including, where appropriate, joint funding of research projects of mutual interest. It is too early to set forth the details of these arrangements but Dr. Butler will discuss his plans when he testifies later in the hearings.

In addition to such diseases as arthritis and diabetes and the broad spectrum of problems that may afflict the aged, many scientific disciplines and fields of clinical study also cut across the categorical missions of all or several of the Institutes. In most cases the necessary coordination is readily achieved through normal disciplinary channels. There are, however, a few fields in which a more deliberate approach to coordination is desirable.

One such field is research on nutrition which is as yet—at NIH and elsewhere—a vast, diverse, and essentially unstructured set of activities. It is, in fact, an undefined field that figures prominently in home economics courses but is not generally recognized as a scientific discipline. In June 1975, NIH established a Nutrition Coordination Committee as a first step in defining the scope of nutrition activities at NIH and developing a focal point for the exchange of information on nutrition. The time is now ripe to extend these activities to monitoring international research on nutrition, identifying gap areas, facilitating collaboration, and selecting specific nutrition research problems for which discrete NIH programs might be developed. We are developing a Nutrition Plan and considering how we might best assess present knowledge on nutrition in order to respond to the increased demand for prudent advice on the optimal diet for maintaining health and contributing to longevity.

Epidemiology, though well defined and long recognized as important to an understanding of the dynamics of disease, has languished partly because of the relatively low status accorded to this discipline, the traditional practice of restricting epidemiology training to graduates of medical schools, and the limited number of adequate training centers. As a result of these factors, there is now a critical shortage of chronic disease epidemiologists, which, unfortunately, coincides with a growing need for sophisticated epidemiologic studies. As a first step



toward rectifying this situation. I have appointed an NIH Epidemiology Committee and have asked them—

To make an estimate, in conjunction with the American Society of Epidemiology, of the current supply of qualified epidemiologists and the future manpower requirements;

To define the basic requirements and suggest a curriculum for training both MD's and non-MD's; and

To explore the desirability and feasibility of establishing a training program at NIH in cooperation with universities and other Federal agencies.

During the past decade, genetics has made the most dramatic strides of any of the biomedical sciences—indeed, of any of the sciences. From a purely disciplinary point of view, coordination is hardly necessary: Investigators in the field are only too eager to keep abreast of each other's work. However, because the potential impact of genetics research on a wide variety of disease problems is so great, we have established an NIH Genetics Coordinating Committee which has sought to define the areas of interest and assess the current extent of involvement of Federal agencies in genetic diseases. The results of this enquiry will be part of the report to be submitted to the Congress in April as required by the National Sickle Cell Anemia, Cooley's Anemia, Tay-Sachs, and Genetic Diseases Act (Public Law 94-278). The NIH Committee has also suggested that the Secretary establish a formally chartered DHEW Interagency Genetics Coordinating Committee, with NIH acting initially as the lead agency, to guide the implementation of the act which calls for many activities—such as screening, treatment, and genetic counseling—that lie outside the purview of NIH.

A particular aspect of genetic research that has recently attracted a lot of public attention—and, on the part of some, considerable apprehension—is the work that is beginning to be done with what is called "recombinant DNA." The dangers of doing this research that have received so much publicity are purely speculative: No one knows whether they really exist but, on the other hand, no one can be certain that they do not. However, to put this matter into perspective it must be borne in mind that changes in DNA—the nucleic acid that is present in all living organisms and determines their inherited characteristics—also occur spontaneously in nature: They have made possible the never ending process of evolution. We are as we are as the result of a long series of changes in the DNA of our biological ancestry—and aberrations or faults in DNA are undoubtedly responsible for inherited disabilities and predispositions to disease. Research on recombinant DNA therefore holds the promise of becoming a powerful tool in the conquest of disease and, ultimately, in the prevention or correction of inherited malfunctions and disabilities. The potential dangers of such research are, I think, no greater—almost certainly considerably less—than the dangers, less than a century ago, of cultivating, in primitive laboratories, the newly discovered bacteria of dread diseases for which there was then no prevention or cure. Nevertheless, it behooves us to heed the adage that it is better to be safe than sorry. We have therefore developed guidelines which are mandatory for all laboratories using recombinant techniques in research conducted by or supported by any Federal agency. These guidelines have also been adopted by the member industries of the Pharmaceutical Manufacturers Association and the international scientific community has reached agreement that a common set of standards shall govern the use of recombinant DNA techniques. The Interagency Committee on Recombinant DNA Research is now considering how this is to be accomplished and how compliance is to be monitored and enforced.

Under proper safeguards much good can flow from this latest development in the steady progress of science. It is probably not an exaggeration to compare our unfolding ability to split and recombine DNA chains to our ability to split atoms—and I believe that the long-term benefits to mankind will be substantially greater. There is good reason to believe that genetic research—of which the present work on DNA is merely the forerunner—will have as sweeping an impact on health and the practice of medicine during the last quarter of this century as the new science of bacteriology had during its first quarter.

But if biomedical research is entering a new era, so is its relationship to society. It is passing from an extended period of relative privacy and autonomy to an engagement with new ethical, legal, and social imperatives under concerned public scrutiny. NIH has responded to this concern by requiring the formation of review boards to oversee human experimentation, animal care, and now genetic recombination experiments. Similar bodies may soon have to oversee other hazardous laboratory work. These responsibilities are inescapable adjustments to the rising demand for public governance of science, though this need

not—and, indeed, should not—go beyond what is clearly required for public safety lest we inadvertently impede successful research and hamper creativity. The progress of science will continue to depend on the initiative and insights—call it inspiration, if you like—of individual scientists. NIH has no intention of trying to mastermind research.

The NIH budget requests now before you total \$2,576,371,000, which is an increase of \$4,957,000 over the comparable figure for fiscal year 1977. A third of the funds requested for the research components are for the Cancer Institute. I am satisfied that the distribution of the remaining funds between the other Institutes is reasonable and that the budget requests, as a whole, will enable NIH to maintain its present level of effort. The Directors of Institutes, Research Divisions and the National Library of Medicine will testify for their respective programs.

Dr. FREDRICKSON. These problems affect the directions in which NIH will move and the manner in which its programs will develop during the next few years. Important among these is the relationship of NIH, as the principal biomedical research agency of the Federal Government, to the health service community and the extent to which NIH can, and should, take responsibility for important activities at the boundary between the conduct of research and the delivery of health services.

#### COMMUNICATION OF RESEARCH RESULTS

Certainly not an issue is the responsibility that NIH clearly has to communicate research results. We have just prepared a report on those activities initiated by NIH during 1976 for improving the dissemination of research results, and I should like to submit a copy for inclusion in the record of these hearings.

Mr. Flood. Without objection, that will be done.

[The report follows:]

#### REPORT ON ACTIVITIES INITIATED BY THE NATIONAL INSTITUTE OF HEALTH DURING 1976 FOR IMPROVING THE DISSEMINATION OF RESEARCH RESULTS

The following report on activities for improving the dissemination of research results describes projects undertaken by the National Institutes of Health since January 1976. Concurrently with the development and initiation of the efforts summarized in the report, the Director, NIH, his staff and the Director's Advisory Committee have devoted considerable time to an assessment of NIH responsibility at the Health Research/Health Care interface. Dissemination of information on findings ready for application to patient care is viewed as an important element of such responsibility.

A plan is in development to establish an overall organizational framework for identifying and fostering the evaluation of new knowledge which is on the verge of transfer to the health care community. The plan will include the design of a permanent organizational structure for the dissemination program.

In considering dissemination improvement projects, priority attention has been given to those involving communication with health professionals engaged in primary care. Such efforts were designed to accelerate the transfer of research findings related to a selected list of clinically significant topics by giving the information "special delivery" treatment, supplemental to its normal diffusion through the channels by which professionals keep informed.

In accordance with the improvement plans previously submitted to the Congress, additional health information materials have been prepared for use by the public media as well, with emphasis on materials for use by radio and television stations. Four public service announcements providing substantive health information have been prepared and distributed to all U.S. radio stations.

A set of dramatized announcements on diabetes and colon cancer is ready for distribution to all TV stations. The NIH produced and distributed to 2,247 high schools a 15-minute health information film accompanied by kits of teaching

PROBLEMS OF CONTROL AND  
REGULATION

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AN OVERVIEW OF THE ROLE OF NIH AND OTHER FEDERAL AGENCIES  
IN THE CONDUCT OF RESEARCH WITH RECOMBINANT DNA

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Donald S. Fredrickson

*Director, National Institutes of Health*

I am very grateful for the opportunity to summarize something about the government process in this matter which you have been discussing throughout this Forum.

Governments in general, and the federal government in particular, entered the matter of recombinant DNA research several years ago when, after Asilomar as you recall, one of the recommendations of the scientists was that the NIH form a committee that might begin to set up guidelines to establish strict conditions for the conduct of research that involved the use and production of recombinant DNA molecules. These guidelines were developed by a recombinant DNA committee, and after extensive scientific and public review the NIH released them on June 23, 1976.

The provisions were designed to afford protection with a wide margin of safety to workers and to the environment. The NIH guidelines were published in the *Federal Register* on July 7, 1976, for public comment.

In September the NIH also filed a draft environmental impact statement on the guidelines for public comment, and the final NIH environmental impact statement we expect to be published shortly. As many of you are aware, in August 1976, a volume was published by the NIH that contains the transcript of a public hearing held on the guidelines as



well as all correspondence received by my office on this matter prior to the release of the guidelines in June. And there will be a subsequent publication of all correspondence and many other related documents to continue this complete public record of government action in regard to recombinant DNA research.

By the time the environmental impact statement had been issued and the guidelines released, it was already apparent that the international community of science had come to agreement that recombinant DNA techniques should be used only with a common set of standards across the world. The question was how to bring this about. And as matters of this sort are often settled, first the boundaries of activity were restricted to those maximum ones in which the law can be operable across a population, and hence most countries settled down to attempt to enter this second phase for themselves before seeking further international comity and conformity with particular standards.

At the time the NIH guidelines were released there was convened by the Secretary of Health, Education, and Welfare an Interagency Committee on Recombinant DNA Research. The committee was formed with the approval of the President, and at the Secretary's request I have served as chairman.

Now, this Interagency Committee is composed of representatives of the federal departments and agencies that do several things. One component is made up of those agencies that support or conduct recombinant DNA research, or may do so in the future. Another group includes the representatives of all the federal departments and agencies that have present or possibly potential regulatory authority in this area. And to these are added a number of other departments, such as the State Department, the Department of Justice, and others that have particular interest in the general aspects of the committee's affairs. There are approximately twenty-five member agencies that make up this committee.

The mandate of the Interagency Committee is to review the nature and scope, particularly of the federal activities, relating to recombinant DNA research. Second, the committee was directed to determine the extent to which the NIH guidelines may currently be applied to research in both the public and the private sectors. It was to recommend, if appropriate, legislative or executive actions necessary to ensure compliance with the standards set for this research, and to provide for the full communication and necessary exchange of information on recombinant DNA research programs and activities throughout the federal sector.

The Interagency Committee held its first full meeting last November, and during that month it had a second meeting. The first of those meetings was held on November 4 and was devoted to a review of the development of the NIH guidelines for research involving recombinant DNA molecules. At the same meeting the committee also reviewed *in extenso* international activities relative to this same matter. I will not repeat that review, because I understand you are to have a report of a workshop which will summarize it for you in much greater detail than I can now. But the committee was fully aware of activities relative to this matter not only in this country but abroad.

At the meeting of the committee held on November 23, the federal research agencies then discussed their activities and possible roles in the implementation of the NIH guidelines. All of the research agencies endorsed the NIH guidelines to cover the recombinant DNA research that they conducted or funded. Three agencies of the federal government are now supporting research that involves the use of these techniques, the NIH, the National Science Foundation, and the Department of Agriculture. The Department of Defense, NASA, and the Energy Research and Development Administration are not at present conducting such research, but agreed to use the NIH guidelines to govern future research should they undertake it.

In that November 23 meeting the federal regulatory agencies also reported on their regulatory functions. Following that lengthy review a special subcommittee was set up to analyze the relevant statutory authorities for the possible regulation of recombinant DNA research. All regulatory agencies were represented on that subcommittee, and their representatives were assisted by attorneys from their offices of general counsel.

The subcommittee was charged to find out whether existing legislative authority would permit the regulation of all recombinant DNA research in the United States, whether it was funded by the government or not, and to seek out whether or not those existing legislative authorities would include at least the following requirements perceived by the committee to be important: review of such research before it is undertaken by an institutional biohazards committee; compliance with physical and biological standards and prohibitions in the NIH guidelines; registration of such research in a national registry; and enforcement of the above requirements through monitoring, inspection, and some sanctions.

It was the conclusion of this subcommittee after extensive review that present law permits imposition of some of the desired requirements on much recombinant DNA laboratory research, but no single legal authority or combination of them currently exists that would clearly cover all research or other uses of recombinant DNA techniques and meet all the other requirements. The committee examined, first of all, the Occupational Safety and Health Act, and found that while OSHA has broad authority it has limited access to many of the laboratories, and it does not cover self-employed persons. The Environmental Protection Agency under the Toxic Substances Control Act is directed to control chemicals that may present an unreasonable risk of injury to the health or the environment. The subcommittee found that probably most recombinant DNA molecules could come under the definition of chemicals; however, Section 5 of the Toxic Substances Act explicitly exempts registration of chemical substances used in small quantities for the purposes of scientific experimentation or analysis. The latter exemption represents the most serious deficiency in the authorities of that act for the purposes of regulating the use and production of recombinant DNA molecules.

The Hazardous Materials Transportation Act was also examined. It gives the Department of Transportation and the Center for Disease Control in Atlanta considerable authority over interstate shipment of hazardous

materials but, indeed, there were many aspects of this act which are wanting in regard to regulation of recombinant DNA research.

The Environmental Defense Fund, in November of 1976 petitioned the DHEW to regulate recombinant DNA research under Section 361 of the Public Health Service Act, and this petition was filed with the Interagency Committee for its consideration. Under this section the authorities are restricted to organisms that are communicable and cause human disease. To use Section 361 for regulatory authority one would have to assume that recombinant DNA research may cause human diseases and that these may be communicable. Further, Section 361 does not apply to plants or animals or the general environment. It was the conclusion of the committee that Section 361 lacks the requisite authorities.

The same is true of Section 353 of the Public Health Service Act. This applies to clinical laboratories, but it is not considered to be applicable to research laboratories.

Many other authorities, particularly of the EPA and of other agencies including the Food and Drug Administration, were examined, as were the powers of the Department of Agriculture, whose authorities were found applicable solely to nonhuman life and plants.

In summary, the Interagency Committee concluded that no single authority or combination of authorities currently exists that could clearly reach all recombinant DNA research in a manner that the committee deemed was appropriate. It was agreed that regulatory actions could be taken under existing authorities, but that they would be in considerable jeopardy of legal challenge.

The full committee then adopted the report of the subcommittee, agreeing with its conclusion about existing authority. It then turned its attention to examining possible new legislation. In considering elements for new legislation the committee reviewed federal, state, and local actions and activities that bear on the regulation of DNA research. In addition to activities in municipalities such as Cambridge, it received a report from the New York State Attorney General's Environmental Health Bureau for State Regulation, which made certain recommendations for regulation in New York State. The committee was aware of the hearings in the California legislature, and it also was able to examine legislation now submitted to the Congress, specifically Senate Bill 621, the DNA Research Act of 1977, introduced by Senator Dale Bumpers, and the companion measure introduced into the House by Mr. Ottinger.

The committee also had available to it comments elicited by its various members from a number of persons whose opinions were sought concerning questions relative to legislation. These sources included agricultural scientists, biomedical scientists, environmentalists, and leaders from labor unions and private industry. In the light of this background the committee has been considering in its most recent meetings what should be the elements of new legislation that might cover the regulation of the use and production of recombinant DNA molecules. It has had to consider issues of definition, the question of registration of all activities, and the question of whether licensure might be an effective part of a regulatory process, and it has dealt strongly with



aspects of interagency cooperation. It also has had to deal with the difference or the distinction between research and commercial use of recombinant DNA products, particularly because many commercial aspects are clearly covered by existing legislation or authority invested in the Environmental Protection Agency and the Food and Drug Administration. It has also had to contend with the fact that the NIH is not a regulatory agency and that it has no intention of becoming one, and that it would be inappropriate for NIH to assume inspection and enforcement authorities when it has participated in standards setting.

The Interagency Committee meets again tomorrow. We expect and hope that it may produce an interim report dealing with some recommendations with respect to legislation within a week. Then the committee will turn to other agenda relative to this problem, and at some point will probably self-destruct when it has carried out fully the terms of its mandate.

In brief, there is a strong and active focus within the executive branch to formulate recommendations to help set federal standards, which I think to be very much needed, with regard to the regulation of the use and production of recombinant DNA molecules. The task has not been simple. The committee has recognized its responsibility to protect fully the public interest. It recognizes that recombinant DNA activities can pose some threat to workers, to the general population, to the environment, and also to a creative and responsible scientific apparatus. Thus, the task of recommending appropriate, effective, and reasonable legislation for regulation of this activity is a matter of very grave concern.

## DISCUSSION

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NORTON ZINDER, Rockefeller University: I would like to support, and I am surprised that I am going to do so, the idea of having legislation, federal legislation, with regard to recombinant DNA research. The proliferation of local option with different guidelines in different states and different cities can only lead to a situation of chaos, confusion, and ultimately to hypocrisy amongst the scientists involved. I strongly plead that the government move ahead on this as rapidly as possible.

FREDRICKSON: Thank you, Dr. Zinder.

AL PLUMMER, retired civil engineer: I am neither for nor against rapid research in recombinant DNA. I am here to learn what the facts are so as a private citizen I can choose sides when it becomes appropriate. I have listened to 85 percent of the discussion, and so far I have not been able to identify who in the federal government is responsible for bringing together in one comprehensive document all the history, facts, alternative pathways, along with calculations, as best they can be made, of benefits and costs and the environmental impacts of this

problem. In other words, who is doing the planning that will point out where we are going so that we as private citizens can make intelligent decisions? Is there a group planning what kind of a program would be appropriate for the nation as a whole? I understand you are dealing with regulation and setting standards, and that is fine, but it doesn't really attack the problem of where we are going with this. Is it good? Is it bad? What are the problems? Can you tell me who is going to come up with a document?

FREDRICKSON: Yes, Mr. Plummer. First of all, several documents have already been issued which may be helpful to you. I referred to two of them. One is the NIH preparation of the history relative to its guidelines. The second is the environmental impact statement issued relative to its guidelines. The Interagency Committee now contains all the elements of the federal supporters and conductors of this research, and probably they are responsible for at least 90 percent of the research that is doubtless going on at the present time in this country. They will be reporting to the Secretary of Health, Education, and Welfare, in whose office now, as this matter ascends higher up in the Department, will be the next focus for disseminating and developing some of the considerations that you represent. A third focus will open up next week when the Congress of the United States will, I think, have the first of a number of hearings on this whole matter of recombinant DNA research. I believe that there are several committee hearings that are scheduled or are about to be, which will deal not only with the matter of legislation, but also the general aspects of the recombinant DNA research. Finally, we have been this week, and I expect to return to, the Appropriations Committee in the House, and the Senate next week, where we have also been answering a number of questions of the kind that you have posed.

PLUMMER: Well, my basic statement is that it is fragmented and it isn't pulled together in such a way that we can quietly analyze it and come to conclusions. As a result I see in this meeting that the opponents and proponents are polarizing and that will lead to emotional situations, and it will get more and more difficult to resolve unless we get the facts all laid out.

DAVID O. KRASSIK, Engineering and Applied Science, UCLA: I am interested in learning more about how one has established the adequacy of the current NIH guidelines. My background is not biology or biochemistry, and I have been listening to try to keep the words *vector*, *phage*, and so forth apart in my mind.

I did go to the containment workshop last night and there tried to find out whether there exist documents that would give details on the efficacy of physical containment and biological containment, but I was told no. I must confess, I was a little surprised at what seemed to be the relative ineffectiveness of P1 to P3 containment, assuming that there is a risk, and I have to rely on my medical and biological colleagues to tell me that.

With regard to the biological containment, again, one hears numbers of large factors, but again, there are uncertainties. So as I listened I found in my own mind no way of knowing as a result of these few days how the guidelines were arrived at, how the kinds of questions raised by Dr. Sinsheimer here at the Forum yesterday and previously have been dealt with or are being dealt with in deciding that these guidelines are adequate, that they are not too strict or not strict enough.

FREDRICKSON: Have you had opportunity to read the NIH guidelines, their appendixes, and all of the comments relative to them?

KRASSIK: Yes, I have, but with my limited background I could only digest part of it.

FREDRICKSON: If you will give us your name at the NIH one of the documents that will be very helpful to you is the revised or final environmental impact draft statement, which has addressed in detail comments of the kind and questions of the kind that you have raised. The development of both the guidelines in their final form and the environmental impact statement have involved an exchange of correspondence and a full attention to a wide range of public comment, each of which has been addressed in the revised document.

FRANCINE SIMRING, Friends of the Earth: I would like to congratulate the NIH and Dr. Fredrickson on the wonderful job they have done of disseminating materials, transcripts, and Xeroxes to all interested parties. And in the interest of expanding the accuracy, I want to make three short additions to what was said by Dr. Fredrickson.

You mentioned, I believe, that all correspondence was included in the yellow volume of August. I believe we would have to make that "some" correspondence in the interest of accuracy.

You mentioned that the nations settled down by themselves to do their guidelines. A few did, but for the most part in the correspondence that I read, many nations wrote to state they are looking to the United States for leadership, and will follow the U.S. guidelines when they are published. In the light of this afternoon's press conference, I think that is particularly important.

The last point that I would like to make is that Dr. Fredrickson mentioned that the Interagency Committee listed registration of such research with a national registry. However, there is a parenthetical opening for industry that reads as follows: "Subject to appropriate safeguards to protect proprietary interests," which means that they might not have to register their projects.

FREDRICKSON: Thank you, Mrs. Simring. I am glad to meet you even at this distance, and I hope to close the gap between us.

Indeed, the volume that I referred to does refer only to correspondence relative to the guidelines. Many of the subsequent letters we



have received will have a broader base because more action has occurred since that time. There will be another issuance. I know that some of your correspondence will also appear there.

With respect to extension of the U.S. guidelines, it is true that there are other countries that are using them, as well as the United Kingdom guidelines. You will hear more about that, I am sure, in the final description.

With respect to the matter of registration and the issue of proprietary information, this is certainly one matter which the Interagency Committee is discussing and will grapple with completely, you can be sure.

AUDIENCE: Dr. Fredrickson, like many people I am beginning to share a mania against federal intrusion into so many aspects, and I think it is rare and unique for the American scientific community to actually invite a federal incursion. Yet, with so many recent experiences, occupational safety and health and what have you, it has been proven that the federal government is probably the least adept. I am happy to see that you are working with the Hill on legislation, but you just mentioned that the NIH doesn't have or want enforcement authority regarding this work. Who would the legislation give it to? HEW? Federal bureaucrats? Who is going to monitor it? I assume that there will be legislation, but I hate to see an element of control removed from the scientific community, and I wonder who they will award it to.

FREDRICKSON: I am not sure to whom it will be awarded either. But you can be sure that this is a matter which the committee is now actively considering and will deal with in its report.

ENVIRONMENTAL HEALTH RESEARCH AT THE  
NATIONAL INSTITUTES OF HEALTH

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HEARING  
BEFORE THE  
SUBCOMMITTEE ON THE  
ENVIRONMENT AND THE ATMOSPHERE  
OF THE  
COMMITTEE ON  
SCIENCE AND TECHNOLOGY  
U.S. HOUSE OF REPRESENTATIVES  
NINETY-FIFTH CONGRESS  
FIRST SESSION

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MARCH 10, 1977

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[No. 28]

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(II)



## CONTENTS

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WITNESSES

	Page
March 10, 1977: Dr. Donald Fredrickson, Director, National Institutes of Health; accompanied by Dr. David Rall, Director, National Institute of Environmental Health Sciences, and Dr. Guy Newell, Acting Direc- tor, National Cancer Institute.....	2 ✓

(III)

STATEMENT OF DONALD FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH, ACCOMPANIED BY DAVID RALL, M.D., DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES; AND GUY NEWELL, M.D., ACTING DIRECTOR, NATIONAL CANCER INSTITUTE

Dr. FREDRICKSON. Thank you, Mr. Chairman. It is a genuine pleasure for us also to be able to meet with the committee this afternoon and to discuss those activities of the National Institutes of Health that contribute to improved understanding of man's environment and its effect on health, and ultimately to the prevention of disease and the promotion of good health.

As Dr. Rall apparently indicated in his testimony on February 23, environmental health is a relatively new area for biomedical science. Biomedical science per se, Mr. Chairman, is a very broad continuum, including research at one end of the fundamental life processes which are continually moved forward, and extended, and resynthesized into ways to practically benefit man, to prevent disease, and to help cure it when it occurs.

I would say personally that I think you could look at our activities in three great generic categories. One is to understand biological systems. The second is to understand how the genetic code determines the fitness of each individual in regard to the functioning of his biological system, and the third is a question of how man and other animals adapt to the environment and ecology in which they live, and that adaptation is dependent both on the nature of the environment and on the genetic structure.

Quite possibly, we have learned much more about biological systems and, indeed, are in the middle of an almost revolutionary period of knowledge about genetic principles that set those processes, and in certain respects, environmental science is indeed the most primitive of the three.

If we exclude certain elements of the environment, cultural elements such as diet or the effects of specific agents such as bacteria in the environment, then indeed we are only in the beginning of an understanding of how chemical and physical forces affect the adaptation of man and his survival.

We are still learning the basic scientific principles upon which theories of the causes and mechanisms of diseases can be built.

The concept that the human body processes or metabolism allows the usage of certain chemical substances and their conversion into completely different substances which may cause tissue or organ damage is a discovery of relatively recent time, and it is clearly not fully understood.

If we are to assess accurately the effects of environmental agents on the human being, we must learn more about these interactions.

The condition of the environment is also a matter of serious concern. Over the past two decades, we have learned that we have much more to fear from the polluted environment than acute respiratory disease or gastrointestinal infections. The effects of long-term continuing exposure to small doses of toxic agents of many types—from tobacco smoke to exotic synthetic chemicals—are believed to be much more profound than we previously understood. The threat of these toxic

agents has been intensified and the effects are exacerbated by the rapid development and introduction into our environment of massive quantities of untested synthetic chemicals over the past 15 years.

Even our most sophisticated techniques and methods are not now sufficient to seek out the chemical hazards in a quick, inexpensive, and conclusive manner or to predict the effects of the various pollution levels, and understand their action singly or in combination.

We anticipate that a continued and concerted basic science effort—the kind of effort the NIH is uniquely suited to accomplish—will be necessary before we have the basis of understanding we need in order to recommend decisive action. We are committed to this effort as a major feature of NIH's program. We sincerely believe that the benefits of this research emphasis will far outweigh the time and financial costs.

Along with NIEHS, which is responsible for seeking new knowledge about a broad range of environmental conditions which adversely affect man's health, and NCI, which is aggressively investigating environmental sources of human cancers, other NIH Institutes which support and conduct research related to specific diseases and life processes must be concerned with the impact of agents in the environment on diseases within their areas of responsibility. Environmental causes appear to be significant factors in pulmonary disease, many chronic neurological disorders, birth defects, and cell mutations.

We believe it is imperative that the NIH be involved in environmental health research. We believe that the mission of the Public Health Service is the appropriate context for this involvement. We are planning to carry out this role in the following ways:

By placing increased emphasis on the search for environmental factors which cause chronic diseases and disorders;

By devoting additional resources to chronic disease epidemiology in recognition that studies of disease patterns in human populations are crucial to inferences regarding the effects of the environment on human health;

By working with the National Center for Health Statistics to establish a national environmental death index;

By strengthening information exchange and data systems concerned with toxicological information;

By placing increased emphasis on research on the effects of toxic agents. This research will improve our understanding of the relationship of these agents to disease, and will enable us to evaluate available toxicologic test methods;

By increasing support for research manpower training in critical areas such as toxicology and epidemiology, which are, as you know, in very short supply; and

By broadening the advisory input to all environmental regulations that may impact on health.

We estimate that in fiscal year 1978, the National Institutes of Health will devote at least \$250 million to environmental health research. This represents over 50 percent of the total Federal financial commitment to environmental health research.

We view our role as important, and the issues related to environmental health as integral to the total NIH mission and responsibility.

I appreciate the opportunity to share this position with the committee. Drs. Rall, Newell, and I will be pleased to answer any questions that you or other members may have.



Mr. BROWN. Thank you. I think that is a very good statement. It gives us a framework in which we can better understand how environmental research is handled, and what some of the programs are that you see as being importantly related to the general needs of environmental control.

Dr. Fredrickson, the last statement you made with regard to the way NIH is involved in this environmental health research is impressive. I would like to find out a little bit more about what lies behind the statement.

Each of your statements refer to programs which you have, I am sure, within NIH. Do you have ways of estimating the resource levels which are devoted to each of these programs, and determining whether they are actually being given increased emphasis or not? In other words, what is the historical resource background in each of these areas? First of all, I am asking if you have this kind of information. Do you have these kinds of breakdowns? I am not asking you to supply an answer to my question now, but I probably will ask you to supply it for the record.

Dr. FREDRICKSON. Yes, Mr. Chairman, we do have a breakdown.

To expand upon my statement with regard to Federal agency support for environmental health research and related programs, information provided by each of the agencies which includes not only the NIH Institutes or Bureaus but also other agencies within the Government—we will be glad to provide such information to you for the record.

## DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

## National Institutes of Health

## Statement by the Director

Mr. Chairman and members of the Committee:

As the Directors of each of the 14 components of NIH for which there are separate appropriations will be here to explain their present activities and future plans, I believe that it is appropriate--and, I hope, helpful to the Committee--for me to discuss briefly

... some activities and problems that concern NIH as a whole;

... what we are doing in areas in which NIH as a whole has new

or expanded legislative mandates; and

... areas that I believe need further development.

The major problems that affect the directions in which NIH will move, and the manner in which its programs will develop, during the next few years are common to all, or most, of the Institutes.

The most important of these common problems is the relationship of NIH, as the principal biomedical research agency of the Federal government, to the health service community--and the extent to which NIH can, or should, take responsibility for activities that lie at the boundary between the conduct of research and the delivery of health services. As clinical research--that is, research involving human patients as distinct from research done solely in the laboratory or with animals--necessarily includes caring for patients, the boundary between research and service is not easy to define. This, of course, complicates any decision on how far NIH should go in carrying out its primary responsibility for the conduct of research.

There can be no doubt that this responsibility includes the communication of research results. Although much of the research supported by NIH, or conducted in its own facilities, is as far removed from the needs at the bedside as exploring for an oilfield is from pumping gasoline into a car, the end product of all the work we do or support is the prevention, cure or amelioration of disease and disability. Due to the complexity of most disease problems, each investigator is, in effect, a sub-contractor working on what is often a very small piece of the problem and his results will usually only be of interest and of use to other investigators working on related pieces. But their collective goal is ultimately to put together information that will have a direct bearing on man's ability to prevent or cope with disease. Research, therefore, is not completed until usable results have been made available to health practitioners and to the general public.

We have just prepared a report on the activities initiated by NIH during 1976 for improving the dissemination of research results. I should like to submit a copy for inclusion in the record of these hearings. It is, in both senses, a progress report: first, because we feel that we have, indeed, made some progress in improving communication with health professionals engaged in primary care, and, secondly, because this is an on-going and expanding activity for which, we hope, a final report will never be written.

In particular, I look forward to the development of the Lister Hill Center for Biomedical Communications to enhance the ability of NIH to play a more effective role--construction of the long-delayed building for this Center is now scheduled to begin in April. The National Library of Medicine, since it became part of NIH, has already moved far beyond the



traditional passive archival role of a library and with the completion of the Lister Hill Center its ability to explore and expand innovative technological approaches to the storage, retrieval and dissemination of information will be greatly enhanced. At the same time, I must point out that communication is not a job that NIH can do alone. Our main mission, and our expertise, is in providing the substance of what must be communicated--and here we must constantly strive to do a better job of selecting and displaying what is immediately useful to practitioners and the public. But other agencies, particularly the professional societies and voluntary health groups, are better situated to reach the wide audience to whom communication must be addressed--they must be encouraged to take a more active part in the bucket brigade carrying knowledge from the research well to the health services.

A more fundamental--and much more complex--problem at the juncture of research and the delivery of health services is how best to transfer the technology developed as the result of research and, more particularly, how to assess or forecast its long-term effects. Many new developments have dangers as well as benefits and they may have economic and social impact as well as purely medical usefulness. Sometimes ethical questions may also arise. In each case, the pluses and minuses must be balanced and the inevitable differences of opinion, even among scientists, must be weighed. To this end, we must seek a technical consensus not merely to determine the clinical significance of new findings but to assess their ethical, social and economic implications. We cannot, in good conscience, widely disseminate research information just because it exists--we must, in so far as is possible, be certain that the full effects, in the broadest sense, of

putting it into practice are understood and that it is accompanied by whatever warnings or safeguards are necessary. A fairly lengthy document on the responsibilities of NIH in this connection is being prepared. A draft has been discussed with the Director's Advisory Committee and is now receiving internal review. It will be published shortly and copies will, of course, be sent to this Committee.

The best assessment tool for the results of most clinical research is the so-called clinical trial--that is, putting a new procedure into practice under previously agreed and carefully monitored conditions. The Cancer and Heart Institutes have special legislative mandates to conduct such trials but they are, in fact, also conducted under the aegis of each of the other Institutes. In Fiscal Year 1975, the latest year for which complete figures are available, NIH supported 755 clinical trials at a cost of \$87.3 million. Some of these trials had already been in progress for several years--in fact, \$209 million had been spent on them prior to 1975--and many would continue for several more years at a projected cost of \$345 million. The total cost of these 755 trials will therefore be about \$642 million. The size, complexity and duration of these trials--and, therefore, their individual cost--varies widely. The most expensive were the 26 trials supported by the Heart Institute which will cost an average of a little over \$15 million each. Over half of these 755 trials were supported by the Cancer Institute but they account for only 20 percent (\$132 million) of the projected cost. The average cost of the clinical trials that were active in 1975 will be about \$850,000.

Our involvement in clinical trials has increased during the past two years and the future support to which we are now committed is higher than it was in 1975. The time has come to decide how much farther and how rapidly we should go.

The first determinant, of course, is what research developments are thought to be ready for clinical trial. This is not always an easy judgment to make and it is here that technical consensus can become particularly important. The public--and, I am sure, the Congress--is anxious that research be brought to its clinical fruition without delay but there can also be real dangers in bringing new techniques into practice too soon. There have been ample tragic warnings that a promising new drug or procedure can do unsuspected harm and it is, I think, abundantly clear that the public interest is best served by prudence and caution. A second factor in planning further trials is, of course, the cost. In this connection, we must consider not only the commitment of future funds for the years it may take to complete the trial but also the difficulty of terminating support when the trial has served its scientific purpose. In too many instances the grant or contract that made the trial possible also had the effect of making possible a service to patients that would, in effect, be terminated when NIH support ceases. With rapidly rising health care cost, ending a trial may raise a serious problem for the institutions in which the trial is being conducted while continuing it would clearly be contrary to the NIH mission and the purpose for which the funds were appropriated. We must, therefore, be careful to enter into costly trials only in circumstances that give assurance that they will produce answers to scientific questions, in a reasonable time, and that the purely service aspect of the clinical work undertaken



will be continued under other auspices when the trial has been completed. As research is the primary role of NIH and the principal justification for its budget requests, we must be constantly on guard not to assume--or appear to assume--responsibilities for health care services which we cannot properly undertake.

Among the new and expanded legislative mandates for NIH, the two that have the broadest impact are those for diabetes and arthritis.

The current NIH obligations for diabetes research total \$76 million which is slightly more than the \$73.3 million recommended for Fiscal Year 1977 by the Diabetes Commission. Of this amount a little over half--\$39.8 million--is in the National Institute of Arthritis, Metabolic and Digestive Diseases which has primary responsibility for diabetes research. But diabetes-related research also accounts for \$11.9 million in the Heart Institute; \$9.1 million in the Eye Institute for diabetic retinopathy; \$4.6 million in the Child Health Institute; \$1.9 million in the Neurology Institute; \$6.4 million in the Division of Research Resources; and lesser amounts, totalling \$2.4 million, in some of the other Institutes. There is, thus, an over-all NIH involvement of considerable magnitude and scope in diabetes research. To ensure that this broad approach is properly coordinated, I have established an NIH Diabetes Coordinating Committee to complement the activities of the inter-agency committee and the Diabetes Board already established under P.L. 93-354. A joint advisory group has been set up by the Heart and Arthritis Institutes to assist in arranging a clinical trial on the efficacy of controlling blood glucose in arresting the development of vascular complications of diabetes. The Arthritis Institute is setting up several other advisory groups on various aspects of its diabetes

program and is arranging a number of conferences and workshops. Existing advisory groups in other Institutes have also appointed subcommittees or are themselves looking into the diabetic aspects of relevant diseases and conditions. The Institute Directors concerned will testify in more detail on their diabetes-related activities.

Research on arthritis is similarly dispersed throughout NIH though in this case the Arthritis Institute continues to carry a larger share of the burden. Our total obligations during Fiscal Year 1977 will be \$30.5 million of which the Arthritis Institute accounts for \$24.7 million. There are, however, relevant research activities in eight of the other Institutes. We are in the process of reviewing all our arthritis-related programs as part of our preparation of the 1979-1983 Forward Plan. When this is completed I shall appoint a coordinating committee similar to the one for diabetes.

The health problems of the aged also cut across the disease-oriented organizational structure of NIH. Dr. Butler--who became the first Director of the National Institute for Aging on May 1, 1976--is therefore much concerned to coordinate the activities of his Institute with the on-going disease-oriented programs at NIH and with other agencies that have responsibilities and programs affecting the aged. It will be our joint endeavor to ensure that, on the one hand, there is no unnecessary overlap or duplication and, on the other hand, that there is optimal cooperation and collaboration including, where appropriate, joint funding of research projects of mutual interest. It is too early to set forth the details of these arrangements but Dr. Butler will discuss his plans when he testifies later in the hearings.

In addition to such diseases as arthritis and diabetes and the broad spectrum of problems that may afflict the aged, many scientific disciplines and fields of clinical study also cut across the categorical missions of all or several of the Institutes. In most cases the necessary coordination is readily achieved through normal disciplinary channels. There are, however, a few fields in which a more deliberate approach to coordination is desirable.

One such field is research on nutrition which is as yet--at NIH and elsewhere--a vast, diverse, and essentially unstructured set of activities. It is, in fact, an undefined field that figures prominently in home economics courses but is not generally recognized as a scientific discipline. In June 1975, NIH established a Nutrition Coordination Committee as a first step in defining the scope of nutrition activities at NIH and developing a focal point for the exchange of information on nutrition. The time is now ripe to extend these activities to monitoring international research on nutrition, identifying gap areas, facilitating collaboration, and selecting specific nutrition research problems for which discrete NIH programs might be developed. We are developing a Nutrition Plan and considering how we might best assess present knowledge on nutrition in order to respond to the increased demand for prudent advice on the optimal diet for maintaining health and contributing to longevity.



Epidemiology, though well-defined and long recognized as important to an understanding of the dynamics of disease, has languished partly because of the relatively low status accorded to this discipline, the traditional practice of restricting epidemiology training to graduates of medical schools, and the limited number of adequate training centers. As a result of these factors, there is now a critical shortage of chronic disease epidemiologists, which, unfortunately, coincides with a growing need for sophisticated epidemiologic studies. As a first step towards rectifying this situation, I have appointed an NIH Epidemiology Committee and have asked them

- ... to make an estimate, in conjunction with the American Society of Epidemiology, of the current supply of qualified epidemiologists and the future manpower requirements;
- ... to define the basic requirements and suggest a curriculum for training both MDs and non-MDs; and
- ... to explore the desirability and feasibility of establishing a training program at NIH in cooperation with universities and other Federal agencies.

During the past decade, genetics has made the most dramatic strides of any of the biomedical sciences--indeed, of any of the sciences. From a purely disciplinary point of view, coordination is hardly necessary: investigators in the field are only too eager to keep abreast of each other's work. However, because the potential impact of genetics research on a wide variety of disease problems is so great, we have established an NIH Genetics Coordinating Committee which has sought to define the areas of interest and assess the current extent of involvement of Federal agencies in genetic

diseases. The results of this enquiry will be part of the report to be submitted to the Congress in April as required by the *National Sickle Cell Anemia, Cooley's Anemia, Tay-Sachs, and Genetic Diseases Act* (P.L. 94-273). The NIH Committee has also suggested that the Secretary establish a formally chartered DHEW Interagency Genetics Coordinating Committee, with NIH acting initially as the lead agency, to guide the implementation of the Act which calls for many activities--such as screening, treatment, and genetic counseling--that lie outside the purview of NIH.

A particular aspect of genetic research that has recently attracted a lot of public attention--and, on the part of some, considerable apprehension--is the work that is beginning to be done with what is called 'recombinant DNA.' The dangers of doing this research that have received so much publicity are purely speculative: no one knows whether they really exist but, on the other hand, no one can be certain that they do not. However, to put this matter into perspective it must be borne in mind that changes in DNA--the nucleic acid that is present in all living organisms and determines their inherited characteristics--also occur spontaneously in nature: they have made possible the never-ending process of evolution. We are as we are as the result of a long series of changes in the DNA of our biological ancestry--and aberrations or faults in DNA are undoubtedly responsible for inherited disabilities and predispositions to disease. Research on recombinant DNA therefore holds the promise of becoming a powerful tool in the conquest of disease and, ultimately, in the prevention or correction of inherited malfunctions and disabilities. The potential dangers of such research are, I think, no greater--almost certainly considerably less--than the dangers, less than a century ago, of cultivating, in primitive laboratories, the newly

discovered bacteria of dread diseases for which there was then no prevention or cure. Nevertheless, it behooves us to heed the adage that it is better to be safe than sorry. We have therefore developed guidelines which are now mandatory for all laboratories using recombinant techniques in research conducted by or supported by any Federal agency. These guidelines have also been adopted by the member industries of the Pharmaceutical Manufacturers Association and the international scientific community has reached agreement that a common set of standards shall govern the use of recombinant DNA techniques. The Interagency Committee on Recombinant DNA Research is now considering how this is to be accomplished and how compliance is to be monitored and enforced.

Under proper safeguards much good can flow from this latest development in the steady progress of science. It is probably not an exaggeration to compare our unfolding ability to split and recombine DNA chains to our ability to split atoms--and I believe that the long-term benefits to mankind will be substantially greater. There is good reason to believe that genetic research--of which the present work on DNA is merely the forerunner--will have as sweeping an impact on health and the practice of medicine during the last quarter of this century as the new science of bacteriology had during its first quarter.

But if biomedical research is entering a new era, so is its relationship to society. It is passing from an extended period of relative privacy and autonomy to an engagement with new ethical, legal, and social imperatives



under concerned public scrutiny. NIH has responded to this concern by requiring the formation of review boards to oversee human experimentation, animal care, and now genetic recombination experiments. Similar bodies may soon have to oversee other hazardous laboratory work. These responsibilities are inescapable adjustments to the rising demand for public governance of science, though this need not--and, indeed, should not--go beyond what is clearly required for public safety lest we inadvertently impede successful research and hamper creativity. The progress of science will continue to depend on the initiative and insights--call it inspiration, if you like--of individual scientists. NIH has no intention of trying to master-mind research.

The NIH budget requests now before you total \$2,576,371,000, which is an increase of \$44,957,000 over the comparable figure for FY 1977. Half of the funds requested for the research components are for the Cancer and Heart Institutes--a total of \$1,222,578,000. I am satisfied that the distribution of the remaining funds between the other Institutes is reasonable and that the budget requests, as a whole, will enable NIH to maintain its present level of effort. The Directors of Institutes, research Divisions and the National Library of Medicine will testify for their respective programs.



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STATEMENT BY  
DR. DONALD S. FREDRICKSON  
DIRECTOR, NATIONAL INSTITUTES OF HEALTH  
ON RECOMBINANT DNA RESEARCH  
BEFORE THE  
SUBCOMMITTEE ON HEALTH AND THE ENVIRONMENT  
OF THE  
HOUSE COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE

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## I. Introduction

I am pleased to appear before you today to discuss Federal policies concerning Recombinant DNA Research. Specifically, I want to tell you about the activities of two organizations—those of the National Institutes of Health and of a recently formed Federal Interagency Committee—that are relevant to such policy development.

Recent scientific developments in genetics, particularly in the last four years, have culminated in the ability to join together genetic materials from different sources in cell-free systems to form recombinant DNA molecules. "DNA"—which is the shorthand way of saying "Deoxyribonucleic Acid"—is the material that determines hereditary characteristics of all known cells. Thus new forms of living material are created with the ability to replicate themselves. From testimony already received, you will be aware that this new and powerful tool of science has generated great hope and excitement, and, concomitantly, many expressions of concern.

Recombinant DNA research offers great promise for better understanding and improved treatment of human diseases. Medical advances through use of this technology include the opportunity to explore complicated diseases and the functioning of cells, to better understand a variety of hereditary defects, and possibly (in the future) to create microorganisms useful in producing medically important compounds for the treatment and control of disease. Aside from the potential medical benefits, a variety of other applications in science and technology are envisioned. An example is the



large-scale production of enzymes for industrial use; and potential benefits in agriculture include the enhancement of nitrogen fixation in certain plants and the biological control of pests, permitting increased food production.

There are risks in this new research area as well as anticipated benefits. A potential hazard, for example, is that the foreign DNA microorganism may alter the host in unpredictable and undesirable ways. Should the altered microorganism escape from containment, it might infect human beings, animals, or plants, causing disease or modifying the environment. Or the altered bacteria might have a competitive advantage, enhancing their survival in some niche within the ecosystem.

Until the potential risks are better delineated and evaluated in light of developing scientific knowledge, the public should expect such research to be conducted under strict conditions ensuring safety. This was the fundamental principle that guided the National Institutes of Health and the Federal Interagency Committee in their deliberations on Recombinant DNA Research--that is, the desire to allow this significant research to continue while protecting man and his environment, to the extent humanly possible, from the effects of potential hazards whose nature is as yet unknown. I would like to review with the Committee the activities of the NIH in developing guidelines to govern this research, and then devote the rest of my testimony to the work of the Interagency Committee.

## II. Development of the NIH Guidelines

Scientists engaged in recombinant DNA research first expressed concern about the potential biohazards at the Gordon Research Conference on Nucleic Acids in July 1973. At their request, the National Academy of Sciences created a committee that outlined restrictions for these types of experiments and organized an international conference to consider this problem further. The committee also called on the NIH to establish an advisory committee to study containment procedures and draft guidelines for the conduct of this research. At the International Conference on Recombinant DNA Molecules held at Asilomar, California, in February 1975, temporary guidelines were issued calling for a moratorium on some experiments but allowing others to proceed with appropriate biological and physical safeguards, pending issuance of NIH guidelines.

In response to the National Academy of Sciences, the NIH Recombinant DNA Molecule Program Advisory Committee (hereafter, the NIH Recombinant Advisory Committee) was established in October 1974 to advise the Secretary of HEW, the Assistant Secretary of Health, and the Director of NIH in accomplishing their tasks. In December 1975, the Committee, after several open meetings and half a dozen working drafts, recommended proposed guidelines to the NIH Director for his review and decision.

To assist the Director in his review of the proposed guidelines, a special meeting of the Advisory Committee to the Director, NIH, was convened in February 1976. Members of the Committee represented not only science but such other disciplines as law, ethics, and consumer

affairs. Comments received from committee members and a number of public witnesses represented a wide range of views. Follow-up written comments were also solicited. In April, the NIH Recombinant Advisory Committee considered these comments from the February meeting, and a number of changes to the guidelines were made. Concurrently, meetings for information exchange were held with representatives from other Federal agencies and private industry as well as with Congressional staffs. Finally, on June 23, 1976, with the approval of the Secretary of HEW and the Assistant Secretary of Health, the NIH issued guidelines to govern the research it supports on recombinant DNA molecules. The NIH Guidelines established strict conditions for the conduct of this research, prohibiting certain types of experiments and requiring special safety conditions for other types. The provisions were designed to afford protection—with a wide margin of safety—to workers and the environment. Two weeks later, on July 7, 1976, the NIH Guidelines—together with a document indicating the basis of decisions by the Director, NIH, on principal issues—were published in the Federal Register for public comment.

Copies of the Guidelines were widely distributed to foreign embassies, medical and scientific journals, NIH grantees and contractors, and major professional research societies.



### III. NIH Activities Following Release of the Guidelines

These include:

#### (1) Office of Recombinant DNA Activities

To facilitate implementation of the Guidelines, the NIH, in June, established the Office of Recombinant DNA Activities: to administer and coordinate intramural and extramural activities at the NIH; to review the institutional biohazards committees and certification statements; and to monitor reports and information concerning accidents, containment, and safety research innovation. This office is also responsible for establishing a national registry of recombinant DNA research which will include the coding of projects from other agencies.

#### (2) Published Proceedings

In August, the NIH published a volume containing the transcript of the February NIH public hearing on the proposed guidelines, as well as related correspondence received by the Director, NIH, and the results of relevant meetings held prior to the release of the guidelines in June. A second volume is planned for publication in late Spring documenting the correspondence that the NIH received on the guidelines, the Environmental Impact Statement, and the Departmental patent policy.

(3) Environmental Impact Statement

The NIH, in accordance with the National Environmental Policy Act of 1969, undertook an environmental impact assessment to review environmental effects, if any, of research that may be conducted under the guidelines. The NIH Guidelines were released prior to the completion of the assessment because they provide greater protection for the public and the environment than the Asilomar Guidelines which they replaced. For example, in a number of instances the NIH Guidelines require more stringent safety and containment measures, extension of the list of prohibited experiments, and a specific ban on the release of recombinant molecules into the environment.

A Draft Environmental Impact Statement was filed and published in the Federal Register on September 9, 1976, to afford additional public review and comment. The draft statement is currently being analyzed and comments received will be responded to in the final Environmental Impact Statement to be published in late March.

#### (4) Department Patent Policy

In June, shortly before the release of the Guidelines, Stanford University and the University of California asked NIH to review DHEW policies relating to the patenting of recombinant DNA research inventions developed under NIH grants or contracts. Under current DHEW patent regulations, invention rights to discoveries developed under the Department's research support are normally allocated in either of two ways:

- The Department may enter into an Institutional Patent Agreement (IPA) with a university or other nonprofit institution that has adequate mechanisms for administering patents on inventions. The IPA provides the institution the first option to own all inventions made in performance of Department grants or contracts, subject to a number of conditions deemed necessary to protect the public interest.
- For those institutions that have not entered into a patent agreement with the Department, determination of ownership is deferred until an invention has been made, at which time an institution may petition the Department for ownership of the invention.

The NIH solicited opinions from a number of different groups in the scientific community and the public and private sectors concerning those departmental patent policies, with respect to recombinant DNA research inventions. An analysis of the issues raised by the commentators is under review by the Federal Interagency Committee.



#### IV. The Interagency Committee on Recombinant DNA Research

I would now like to devote the remainder of my testimony to the activities of the Interagency Committee on Recombinant DNA Research. This Committee was created, with the approval of the President, to address extension of the NIH Guidelines beyond the NIH, to the public and private sectors.

The specific mandate of the Interagency Committee is as follows: to review the nature and scope of all recombinant DNA research conducted in the United States, to determine the applicability of NIH standards to the government of this research nationally, and to recommend mechanisms to ensure that the standards are being complied with. The Committee is advisory to the Secretary of Health, Education, and Welfare. It includes representatives of Federal Departments and Agencies that support and conduct recombinant DNA research (or may do so in the future), and representatives of Federal Departments and Agencies that have present or potential regulatory authority in this area. At the Secretary's request, I serve as Chairman of the Committee.

Two meetings of the Committee were held in November 1976. The first of these, on November 4, was devoted to a review of the development of the NIH Guidelines. The Committee also reviewed activities in other countries on the development of guidelines for this research. Recombinant DNA research is being conducted in a number of countries, including Canada, the United Kingdom, the Scandinavian countries, most other parts of western Europe, eastern Europe, the Soviet Union, and Japan.

In many countries, appropriate governmental or scientific bodies have reviewed the research and have agreed that it should proceed. Several of the countries have acted to establish guidelines to govern the conduct of this research, including the United Kingdom and Canada. In the United Kingdom, a parliamentary committee addressed the issue and indicated that work in this area should continue under appropriate safety conditions. Scientific advisory committees of international organizations, such as the World Health Organization, the International Councils of Scientific Unions, and the European Molecular Biology Organization, have made similar recommendations.

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At the meeting of the Committee held on November 23, the Federal research agencies discussed their activities and possible roles in the implementation of the NIH Guidelines. All research agencies endorsed the Guidelines to govern recombinant DNA research. At present, the NIH, the

National Science Foundation, the Veterans Administration, and the U.S. Department of Agriculture are supporting or conducting such research. The Department of Defense, National Aeronautics and Space Administration, and the Energy Research and Development Administration do not at present conduct such research, but all have endorsed the NIH Guidelines to govern future research should it be undertaken.

#### Subcommittee Review of Existing Legislation

At the November 23 meeting, the Federal regulatory agencies reported on their regulatory functions. Following that review, a special Subcommittee was formed to analyze the relevant statutory authorities for the possible regulation of recombinant DNA research. All regulatory agencies were represented on the Subcommittee, assisted by attorneys from their offices of general counsel.

The Subcommittee was charged to determine whether existing legislative authority would permit the regulation of all recombinant DNA research in the United States (whether or not federally funded) and would include at least the following regulatory requirements:

- (1) Review of such research before it is undertaken by an institutional biohazards committee.
- (2) Compliance with physical and biological containment standards and prohibitions in the NIH Guidelines.
- (3) Registration of such research with a national registry at the time this research is undertaken (subject to appropriate safeguards to protect proprietary interests).



- (4) Enforcement of the above requirements through monitoring, inspection, and sanctions.

It was the conclusion of the Subcommittee that present law could permit imposition of some of the above requirements on much recombinant DNA laboratory research, but that no single legal authority or combination of authorities currently existed that would clearly reach all research and other uses of recombinant DNA techniques and meet all stated requirements. Although there is existing authority that might be interpreted broadly to cover most of the research at issue, it was generally agreed that regulatory actions taken on the basis of any such interpretation would probably be subject to legal challenge. The Subcommittee, in reaching this conclusion, reviewed the following laws that were deemed to warrant detailed consideration:

- (a) The Occupational Safety and Health Act of 1970 (Public Law 91-596)
- (b) The Toxic Substances Control Act (Public Law 94-469)
- (c) The Hazardous Materials Transportation Act (Public Law 93-633)
- (d) Section 361 of the Public Health Service Act (42 U.S.C. 264).

The full Committee adopted the report of its Subcommittee and agreed that new legislation was required.

#### Interagency Committee Analysis of Elements for Legislation:

In considering the elements for legislation, the Committee reviewed

Federal, State, and local activities bearing on the regulation of recombinant DNA research. Among Congressional proposals reviewed were Senate Bill 621, "The DNA Research Act of 1977," introduced by Senator Dale Bumpers, and the companion measure introduced by Representative Richard L. Ottinger in the House (H.R. 3591). The Committee also noted the resolution introduced by Representative Ottinger on January 19, 1977 (H. Res. 131), requesting DHEW to regulate recombinant DNA research under Section 361 of the PHS Act.

Hearings held by State and local governments, including State legislatures, were among State and local activities reviewed. Recommendations by the New York State Attorney General's Environmental Health Bureau for State regulation, and by the Cambridge (Massachusetts) City Council for city regulation, were also considered.

Several committee representatives also reported on meetings with other interested parties whose views had been solicited on legislation to regulate recombinant DNA research. Those who were contacted include agricultural scientists, biomedical scientists, environmentalists, labor unions, and private industry. At my request, the Industrial Research Institute and the Pharmaceutical Manufacturers Association are surveying their member firms to determine the scope of the research efforts in the private sector. The Pharmaceutical Manufacturers Association has adopted the NIH Guidelines as standards for conduct of this research.

In considering elements of proposed legislation, a number of issues were raised and discussed fully by the Committee. After detailed deliberations at meetings on March 10 and 14, 1977, the Committee agreed on a set of elements for proposed legislation. The elements agreed upon and the various alternatives reviewed by the Committee were presented in an Interim Report transmitted to HEW Secretary Califano on March 15, 1977. Secretary Califano, in releasing the report on March 16, stated that "legislation in this area would represent an unusual regulation of activities affecting basic science but the potential hazards posed by recombinant DNA techniques warrant such a step at this time." The Secretary added that the Department will begin immediately to draft legislation in the light of the recommendations made by the Committee.

Mr. Chairman, I would like to submit for the record this "Interim Report of the Federal Interagency Committee on Recombinant DNA Research on Suggested Elements for Legislation."



#### IV. Conclusion

This much is clear: the international scientific community is in substantial agreement that, until the potential hazards of recombinant DNA techniques are better understood, a common set of standards must everywhere exist for the use of those techniques. The question being debated now is how this is to be accomplished.

In attempting to settle a question such as this, it is natural for society to look first along lines of maximum common boundaries of governance or law. For recombinant work, these have so far been national boundaries. The United States and the United Kingdom were first to develop guidelines; Western Europe, acting initially as individual nations, is beginning to organize a common process; and now Canada has issued a set of guidelines. The substance of all guidelines is sufficiently similar; how to apply them locally and nationally remains the issue.

In the United States, this question has attracted far more public attention than in other countries. A number of local jurisdictions or states are engaged in action or debate. Federal action would assure commonality, if commonality is desirable.

A final point to bear in mind is that changes in DNA--the nucleic acid that is present in all living organisms and determines their inherited characteristics--also occur spontaneously in nature: they have made possible the never-ending process of evolution. We are as we are as the result of a long series of changes in the DNA of our

biological ancestry--and aberrations or faults in DNA are undoubtedly responsible for inherited disabilities and predispositions to disease. Under proper safeguards, much good can flow from this latest development in the steady process of science. Research on recombinant DNA holds the promise of becoming a powerful tool in the conquest of disease and, ultimately, in the prevention or correction of inherited malfunctions and disabilities.

In conclusion, I want to note that biomedical research is entering a new era in its relationship to society. It is passing from an extended period of relative privacy and autonomy to an engagement with new ethical, legal, and social imperatives under concerned public scrutiny. NIH has responded to this concern by requiring the formation of review boards to oversee human experimentation, animal care, and now genetic recombination experiments. Similar bodies may soon have to oversee other hazardous laboratory work. These responsibilities are inescapable adjustments to the rising demand for public governance of science, though this need not--and, indeed, should not--go beyond what is clearly required for public safety lest we inadvertently impede successful research and hamper creativity. The progress of science will continue to depend on the initiative and insights--call it inspiration, if you like--of individual scientists.

# SCIENCE POLICY IMPLICATIONS OF DNA RECOMBINANT MOLECULE RESEARCH

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HEARINGS  
BEFORE THE  
SUBCOMMITTEE ON  
SCIENCE, RESEARCH AND TECHNOLOGY  
OF THE  
COMMITTEE ON  
SCIENCE AND TECHNOLOGY  
U.S. HOUSE OF REPRESENTATIVES  
NINETY-FIFTH CONGRESS  
FIRST SESSION

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MARCH 29, 30, 31; APRIL 27, 28; MAY 3, 4, 5, 25, 26;  
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# CONTENTS

## WITNESSES

	Page
March 29, 1977:	
Dr. Maxine Singer, Laboratory of Biochemistry, National Cancer Institute, National Institutes of Health, Bethesda.....	22
Dr. Emmett Barkley, Director, Office of Research Safety, National Cancer Institute, National Institutes of Health, Bethesda.....	34
Dr. Roy Curtiss III, professor, Department of Microbiology, University of Alabama School of Medicine, Birmingham.....	40
Dr. Charles Lewis, Staff Scientist, Agricultural Research Service, Beltsville.....	49
Dr. George Wald, professor of biology and nobel laureate, Harvard University, Cambridge.....	62
March 30, 1977:	
Dr. Ronald E. Cape, president, Cetus Corp., Berkeley, Calif.....	90
Dr. Daniel Nathans, professor, Department of Microbiology, the Johns Hopkins University School of Medicine, Baltimore, Md.....	122
Dr. Ethan Signer, professor of biology, Massachusetts Institute of Technology, Cambridge, Mass.....	133
Dr. Liebe Cavalieri, researcher, Sloan-Kettering Institute for Cancer Research, Rye, N.Y.....	139
Dr. David Baltimore, American Cancer Society research, professor of microbiology, Massachusetts Institute of Technology, Cambridge, Mass.....	158
March 31, 1977:	
Dr. Donald Fredrickson, Director, National Institutes of Health, Bethesda, Md., accompanied by: Mr. Joseph Hernandez, Division of Legislative Analysis, NIH; Dr. Bernard Talbot, Special Assistant for Intramural Affairs, NIH; Dr. William Gartland, Director Office of Recombinant DNA Activities, NIH.....	188 ✓
Dr. William J. Whelan, chairman, Department of Biochemistry, University of Miami School of Medicine, Miami, Fla.; chairman, committee on Genetic Experimentation.....	293
April 27, 1977:	
Dr. George Pieczenik, Nelson Biological Laboratory, Rutgers State University.....	334
Dr. Robert J. Ryan, Department of Molecular Medicine, Mayo Medical School.....	341
Dr. Patricia Charache, Johns Hopkins Hospital.....	349
Dr. Samuel Formal, Chief, Department of Bacterial Diseases, Walter Reed Army Institute of Research.....	352
April 28, 1977:	
Dr. John G. Adams, vice president, Scientific and Professional Relations, Pharmaceutical Manufacturer Association; accompanied by Bruce J. Brennan, vice president and general counsel, legal, Pharmaceutical Manufacturers Association.....	371
Dr. Irving S. Johnson, vice president of research, Lilly Research Laboratories, accompanied by John M. Holt, secretary and general counsel.....	433

189



FOR RELEASE UPON DELIVERY

DEPARTMENT OF HEALTH, EDUCATION AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20814

STATEMENT BY

DONALD S. FREDRICKSON, M.D.

DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ON RECOMBINANT DNA RESEARCH

BEFORE THE

SUBCOMMITTEE ON SCIENCE, RESEARCH, AND TECHNOLOGY

OF THE

HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY

MARCH 31, 1977



# I. INTRODUCTION

Good day, Mr. Chairman and other Committee members. I am pleased to appear before you today to discuss Federal policies concerning recombinant DNA techniques. Specifically, I want to tell you about the activities of two organizations—the National Institutes of Health and the Federal Interagency Committee on Recombinant DNA Research.

Recent scientific developments in genetics, particularly in the last four years, have culminated in the development of a powerful new tool for research—the ability to join together genetic materials from different sources in cell-free systems to form recombinant DNA molecules. I would like to emphasize the point that recombinant DNA is a tool for accomplishing the types of research that scientists have been pursuing for decades. "DNA"—which is the shorthand way of saying "deoxyribonucleic acid"—is the material that determines hereditary characteristics of all known cells. Thus altered cells are created with the ability to replicate themselves. From testimony already received, you are aware that this new and powerful tool of science has generated great hope and excitement and, concomitantly, many expressions of concern.

Research using recombinant DNA techniques offers great promise for better understanding and improved treatment of human diseases. Medical advances through use of this technology include the opportunity to explore complicated diseases and the functioning of cells, to better understand a variety of hereditary defects, and possibly (in the future) to create microorganisms useful in producing medically important substances for the treatment and control of disease. Aside from

potential medical benefits, a variety of other applications in science and technology are envisioned. An example is the large-scale production of enzymes for industrial use; and potential benefits in agriculture include the enhancement of nitrogen fixation in certain plants and the biological control of pests, permitting increased food production.

There may be risks in this new research area as well as anticipated benefits. A potential hazard, for example, is that the foreign DNA microorganism may alter the host in unpredictable ways. Should the altered microorganism escape from containment, it might infect human beings, animals, or plants, causing disease or modifying the environment.

Until the potential risks are better delineated and evaluated in light of developing scientific knowledge, the public should expect such research to be conducted under strict conditions ensuring safety. This was the fundamental principle that guided the National Institutes of Health and the Federal Interagency Committee in their deliberations. That is, the desire to allow this significant research to continue while protecting humans and the environment from the effects of potential hazards whose nature and the occurrence of which is as yet uncertain. I would like to review with the Committee the activities of the NIH in developing guidelines to govern this research, and then devote the rest of my testimony to the work of the Interagency Committee.

## II. DEVELOPMENT OF THE NIH GUIDELINES

The first step in the development of the Guidelines was taken by the scientific community. Scientists engaged in research using recombinant DNA technology first expressed concern about the potential biohazards at the Gordon Research Conference on Nucleic Acids in July 1973. At their request, the National Academy of Sciences created a committee that called for a moratorium on certain types of experiments and for an international conference to consider this problem further. The committee also called on the NIH to establish an advisory committee to study containment procedures and draft guidelines for the conduct of this research. At the International Conference on Recombinant DNA Molecules held at Asilomar, California, in February 1975, temporary guidelines were issued, including a continued moratorium on some experiments but allowing others to proceed with appropriate biological and physical safeguards, pending issuance of NIH guidelines.

The NIH Recombinant DNA Molecule Program Advisory Committee was established in October 1974 to advise the Director of NIH. In December 1975, the Committee, after several open meetings, recommended proposed guidelines for my review and decision.

To assist me in the review of the proposed guidelines, a special meeting of the NIH Advisory Committee was convened in February 1976. Members of the Committee represented not only science but such other disciplines as law, ethics, and consumer affairs. Comments received from committee members and a number of public witnesses represented a



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### III. NIH ACTIVITIES FOLLOWING RELEASE OF THE GUIDELINES

Subsequent to the release of the Guidelines, NIH initiated several actions.

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To facilitate implementation of the Guidelines, the NIH, in June 1976, established the Office of Recombinant DNA Activities: to administer and coordinate intramural and extramural activities at the NIH; to review the institutional biohazards committees; and to monitor reports and information concerning accidents, containment, and safety research innovation.

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#### IV. THE INTERAGENCY COMMITTEE ON RECOMBINANT DNA RESEARCH

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- (b) The Toxic Substances Control Act (Public Law 94-469)
- (c) The Hazardous Materials Transportation Act (Public Law 93-633)
- (d) Section 361 of the Public Health Service Act (42 U.S.C. 264).

In addition, several other laws were examined. The Clean Air Act, the Federal Water Pollution Control Act, the Resources Conservation and Recovery Act, and the authorities of the FDA and the Department of Agriculture.

The full Committee adopted the report of its Subcommittee and agreed that new legislation was required.

B. Interagency Committee Analysis of Elements for Legislation

In considering the elements for legislation, the Committee reviewed Federal, State, and local activities bearing on the regulation of recombinant DNA research.

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Among State and local activities reviewed were recommendations by the New York State Attorney General's Environmental Health Bureau for State regulation, and the Cambridge (Massachusetts) City Council's resolution on recombinant DNA research.

Several committee representatives also reported on meetings with other interested parties whose views had been solicited on legislation to regulate recombinant DNA research. Those who were contacted include agricultural scientists, biomedical scientists, environmentalists, labor unions, and private industry. At my request, the Industrial Research Institute and the Pharmaceutical Manufacturers Association are surveying their member firms to determine the scope of the research efforts in the private sector. The Pharmaceutical Manufacturers Association has endorsed the NIH Guidelines as standards for conduct of this research.

In considering elements of proposed legislation, a number of issues were raised and discussed fully by the Committee. After detailed deliberations at meetings on March 10 and 14, 1977, the Committee agreed on a set of elements for proposed legislation. The elements agreed upon and the various alternatives reviewed by the Committee were presented in an Interim Report transmitted to HEW Secretary Califano on March 15, 1977. Secretary Califano, in releasing the report on March 16, stated that "legislation in this area would represent an unusual regulation of activities affecting basic science but the potential hazards posed by recombinant DNA techniques warrant such a step at this time." He went on to say, "...I believe such a measure is necessary not just to safeguard the public but also to assure the continuation of basic research in this vital scientific area. We are not saying that research should be halted. We are urging that it should proceed under careful safeguards unless and until we have a better understanding of the



risks and benefits posed by use of recombinant DNA techniques without Government regulation."

The Department is now drafting legislation in the light of the recommendations made by the Committee. This legislation should be ready soon.

Mr. Chairman, I would like to submit for the record the Federal Interagency Committee's "Interim Report on Suggested Elements for Legislation," along with a copy of the Secretary's press release.

With your permission, I would like to review briefly some of the major elements addressed by the Committee. The Committee determined that the Department of Health, Education, and Welfare is the appropriate locus in the Government for the regulation of the use and production of recombinant DNA molecules. In reaching this determination, the Committee took into account existing roles of certain agencies within DHEW—for example, that of the NIH in developing the Guidelines, and of the Center for Disease Control and Bureau of Biologics (FDA) in regulating infectious agents and biological products. The Committee also had before it the petition by the Environmental Defense Fund, requesting DHEW to issue regulations for recombinant DNA research.

The Committee reviewed at great length the nature and scope of regulation. Consideration was given to regulation of all laboratory research where hazardous or potentially hazardous substances were employed. There was general Committee agreement that present legislation should be restricted to recombinant DNA techniques.

However, I have established a committee at the NIH, chaired by Dr. Richard Krause, Director, NIAID, to study and recommend, if necessary, safety standards for other NIH-supported research involving actual or potential biohazards. The preliminary report is expected shortly, and I will keep the Committee informed of the progress on this NIH review.

Regulation of just the research aspects of recombinant DNA techniques presents a problem because of the difficulty in determining the border between research and pilot production. Therefore, the Committee recommends that regulation cover the production or use of recombinant DNA molecules. Such language would include research activity, and makes immaterial possible concerns whether a given activity constitutes research, pilot production, or manufacture. The Committee recommends that the Secretary, in specific instances, in consultation with appropriate regulatory agencies, be allowed to determine the nature of the activity and should defer to a regulatory body that the Secretary determines is better empowered and equipped to deal with it.

There was general agreement by the Committee that registration of projects involving the use or production of recombinant DNA molecules was necessary. The Committee also recommends that facilities be licensed and that the terms of the license include acceptance of responsibility for the particular activities and individuals at the facility. The Committee concluded that licensure of the facility and registration of projects would be more feasible and would more adequately meet the needs

for safety monitoring rather than licensure or registration of individuals engaged in research.

The Committee urges full disclosure to the appropriate regulatory body of all relevant safety and scientific information pertaining to the use or production of recombinant DNA molecules. However, the Committee recognizes the important world-wide commercial potential of recombinant DNA molecules in medicine, agriculture, and other areas of science and technology. It believes that the potential commercial uses of recombinant DNA techniques require that information of a proprietary nature and patent rights be given appropriate protection from disclosure by the regulatory agency receiving such information. However, the Secretary may immediately release information if public safety requires it.

Because the potential hazards posed by the use of recombinant DNA techniques extend beyond the local to the national and international levels, the Committee recommends that a single set of national standards must govern and that, accordingly, local law should be preempted to ensure national standards and regulations. The Committee, however, took into account the activities at the State and local levels on regulation of recombinant DNA research. It was agreed that, if a State passes a law imposing requirements identical to those contained in the Federal legislation, then the Secretary may enter into an agreement with the State to utilize its resources to assist the Secretary in carrying out his duties.

205

16

Protection of workers was also considered by the Committee.

Training of workers in proper laboratory techniques and long-term medical monitoring are important aspects of worker safety and were endorsed by the group.

A number of other recommendations are made, and I can discuss them further if you have questions. I would like to emphasize that the work of the Interagency Committee has been done in a most cooperative and helpful way.

DHEW will continue to cooperate and coordinate with relevant Federal Departments and Agencies in this important matter.

#### IV. CONCLUSION

In conclusion, this much is clear: the international and national scientific community is in substantial agreement that, until the potential hazards of recombinant DNA techniques are better understood, a common set of standards must everywhere exist for the use of those techniques. The question being debated now is how this is to be accomplished. The substance of all guidelines is sufficiently similar; how to apply them locally and nationally remains the issue.

In the United States, this question has attracted far more public attention than in other countries. A number of local jurisdictions or states are engaged in action or debate.



Finally, I want to note that biomedical research is entering a new era in its relationship to society. It is passing from an extended period of relative privacy and autonomy to an engagement with new ethical, legal, and social imperatives under concerned public scrutiny. NIH has responded to these concerns by requiring the formation of review boards to oversee human experimentation, animal care, and now DNA recombinant experiments. Similar bodies may soon have to oversee other hazardous laboratory work. These responsibilities are inescapable adjustments to the rising demand for public governance of science, though this need--and, indeed, should not--go beyond what is clearly required for public safety lest we inadvertently impede successful research and hamper creativity. The progress of science will continue to depend on the initiative and insights--call it inspiration, if you like--of individual scientists.

Dr. FREDRICKSON. I should like to summarize briefly some of the elements in that larger statement which has been submitted for the record.

Mr. Chairman, I am pleased today to be able to appear before you to discuss Federal policies concerning recombinant DNA techniques.

Specifically, I should like to tell you about the activities of two organizations—the National Institutes of Health and the Federal Interagency Committee on Recombinant DNA Research.

Recent scientific developments in genetics, particularly in the last 4 years, have culminated in the development of a powerful new tool for research—that is the ability to join together genetic materials from different sources in cell-free systems to form what are called recombinant DNA molecules. I would like to emphasize the point that recombinant DNA is a tool for accomplishing certain types of research that scientists have been pursuing for decades.

From the testimony already received, you are aware that this new technology has generated great hope and excitement and, concomitantly, many expressions of concern.

Research using recombinant DNA techniques offers great promise. But there may be risks as well. Until these potential risks are better delineated and evaluated in light of developing scientific knowledge, the public should expect such research to be conducted under strict conditions insuring safety. This was the fundamental principle that guided the National Institutes of Health and the Federal Interagency Committee in their deliberations, that is, the desire to allow this significant research to continue while protecting humans and the environment from the effects of potential hazards whose nature and occurrence is as yet uncertain.

I would like to review briefly with the committee the activities of the NIH in developing guidelines to govern this research, and then devote the rest of my statement to the work of the Interagency Committee.

The first step in the development of the guidelines was taken by the scientific community. Scientists who were engaged in research using recombinant DNA technology first expressed concern about the potential biohazards at a Gordon Research Conference on Nucleic Acids which was held in July 1973.

At the request of the attendees at that meeting, the National Academy of Sciences created a committee that called for a moratorium on certain types of experiments and for an international conference to consider the problem further.

The committee also called on the NIH to establish an advisory committee to study containment procedures and draft guidelines for the conduct of this research.

At the International Conference on Recombinant DNA Molecules held at Asilomar, Calif., in February 1975, temporary guidelines were issued including a continued moratorium on some experiments while allowing others to proceed with appropriate biological and physical safeguards, pending issuance of NIH guidelines.

The NIH Recombinant DNA Molecule Program Advisory Committee—Recombinant Advisory Committee—was established October 1974 to advise the Director of NIH. In December 1975, the committee, after several open meetings, recommended proposed guidelines for my review and decision.

To assist me in the review of the proposed guidelines, a special meeting of the advisory committee to the Director, NIH, was convened on February 1976. Members of this committee—which is to be distinguished from the Recombinant Advisory Committee—represented not only science but such other disciplines as law, ethics, and consumer affairs.

Comments received from committee members and public witnesses represented a wide range of views. Follow-up written comments were also solicited from several diverse viewpoints, including the Environmental Defense Fund.

In April, the NIH Recombinant Advisory Committee considered these comments developed from the February session and comments made thereafter, and a number of changes to the guidelines were made. Concurrently, meetings for information exchange were held with representatives from other Federal agencies and private industry, as well as with congressional staffs.

Finally, on June 23, 1976, with the approval of the Secretary of HEW and the Assistant Secretary of Health, the NIH issued guidelines to govern the research it supports involving recombinant DNA molecules. The NIH guidelines established strict conditions for the conduct of this research. The guidelines prohibit certain types of experiments and require special safety conditions for other types. The provisions are designed to afford a wide margin of safety to workers and the environment.

Two weeks later, on July 7, 1976, the NIH guidelines—together with a document indicating the basis of my decisions on the principal issues—were published in the Federal Register for public comment.

Over 40,000 copies of the guidelines have been widely distributed to foreign embassies, medical and scientific journals, NIH grantees and contractors, and major professional research societies.

Subsequent to the release of the guidelines, NIH undertook several actions. To facilitate implementation of the guidelines, the NIH, in June 1976, established the Office of Recombinant DNA Activities to administer and coordinate intramural and extramural activities at the NIH; to review the institutional biohazards committees which are required by the guidelines; and to monitor reports and information concerning accidents, containment, and safety research innovation.

I would like to devote the remainder of my statement to the activities of the Interagency Committee on Recombinant DNA Research. This committee was created, with the approval of President Ford, to address extension of the NIH guidelines beyond the NIH, to the public and private sectors.

The first meeting of the committee, on November 4, 1976, was devoted to a review of the development of the NIH guidelines. The committee also reviewed activities in other countries on the development of guidelines for this research. Recombinant DNA research is being conducted in a number of countries, including most parts of Western Europe, Eastern Europe, the Soviet Union, and Japan.

In many countries, appropriate governmental or scientific bodies have reviewed the research and have agreed that it should proceed. Several of the countries, including the United Kingdom and Canada, have acted to establish their own guidelines to govern the conduct of this research.



If I might digress a moment I would like to expound a bit further, Mr. Chairman, on the activities abroad, because they bear importantly on activities at home.

We have at NIH, through other agencies in our Government and through many scientific societies, been in close contact with many of the scientists and many of the officials abroad who engage in activities, either research or administrative, that relate to the use of these techniques.

Last fall I was privileged to visit a number of molecular biology laboratories in Europe. I stopped in Britain to discuss the Williams report, which is the basis for the United Kingdom guidelines. I talked to members of the European Science Foundation, which is the organization within the European Economic Community that has taken the lead in attempting to have a uniform type of procedure governing the use of these techniques throughout Europe.

We also have been in contact with the genetic manipulation advisory groups of a number of countries. These GMAGs are the operating units that were established under the United Kingdom guidelines adopted by the European Science Foundation as a structure for organizing control of these activities throughout the EEC. We have been in contact with these GMAG's from a number of countries and, most particularly, we had very close contact with Sir Gordon Wolstenholme, who is the chairman of the United Kingdom GMAG.

Chairman THORNTON. Is the formulation of policy in the European countries a matter of public debate, or is this work being done primarily through the institutions of Government and scientific organizations?

Dr. FREDRICKSON. The work has been carried out almost entirely by a group of advisory committees, some of them quasi-governmental, some of them actually private but reporting to governments. There has been very little public debate or press comment, about recombinant DNA activities in Europe, nothing comparable to that which has occurred in the United States.

There has been one question raised in the Swiss Parliament, for example, in the last 3 years, which was quickly answered by the Government.

There have been, on the other hand, almost none of the activities that have attended the development of guidelines in this country. Perhaps it's just a different manner of approaching these problems in the rest of the world.

But I would say that the activities within the scientific community have been very uniform. That is complete agreement across the world of molecular biologists and others who are using these techniques, that it's extremely important to have a uniform set of standards throughout the world.

Chairman THORNTON. Are you suggesting that the assessment of risks of which experiments may be more dangerous and require increasing levels of containment or might be prohibited altogether, that these standards are rather uniformly accepted by the scientific community and the several nations which are conducting the research?

Dr. FREDRICKSON. Yes I am, Mr. Chairman. The United States or NIH guidelines, the United Kingdom guidelines, and the Canadian guidelines, in general, as they deal with recombinant DNA research, are all children of Asilomar. That is, they have been based on the ac-



ceptance of a generally uniform method of prescribing containment for experiments according to the same design as you see in the NIH guidelines.

Chairman THORNTON. Thank you, Dr. Fredrickson.

Please continue with your statement.

Dr. FREDRICKSON. In fact, this agreement among scientists now leaves us at the second stage of development in this problem, and that is how to extend these guidelines throughout the world, how to compel compliance with them.

We find all nations dealing individually with this problem because a single country offers the largest political unit in which law can be applied effectively in dealing with these problems.

With the effective development of statutes or application of available and existing regulations, it should be possible to blanket the whole world with a quite uniform set of standards of conduct for the use of these techniques.

We have also been in indirect contact, through the International Council of Scientific Unions, with scientists, and molecular biologists in the Eastern European countries, including Professor Bayev, who is head of the Soviet Academy of Science Committee which is seeking to develop guidelines for use in the Soviet Union. Throughout all of these countries, the NIH guidelines and United Kingdom guidelines are being used, together or alternately, and thus there is really a quite uniform standard of conduct at the present time.

In addition to reviewing the activities abroad, the Interagency Committee at its November 4 meeting also had the Federal research agencies discuss their activities and possible role in the implementation of common guidelines. All of the research agencies endorsed the guidelines.

At the meeting on November 23, 1976, of the Interagency Committee, the Federal regulatory agencies reported on their regulatory functions, as they might relate to the use of recombinant DNA techniques. Following that review, a special subcommittee was formed to analyze the relevant statutory authorities for the possible regulation of research involving recombinant DNA technology. All regulatory agencies were represented on this subcommittee, and assisted by attorneys from their offices of general counsel.

It was the conclusion of the subcommittee that no single legal authority or combination of authorities currently exist that would clearly reach all research and other uses of recombinant DNA techniques.

The full committee reviewed the findings of the subcommittee and adopted its report, and agreed that new legislation is needed.

The committee then turned to considering the elements for possible new legislation, and in doing so, it reviewed Federal, State, and local activities bearing on the regulation of recombinant DNA research.

Additionally, the views of several interested parties were solicited on legislation to regulate recombinant DNA research. Those parties included agricultural scientists, biomedical scientists, environmentalists, labor unions, and private industry.

After detailed deliberations at meetings on March 10 and 14, 1977, the committee agreed on a set of elements for proposed legislation. The elements agreed upon and the various alternatives reviewed by

the committee were presented in an interim report which was transmitted to HEW Secretary Califano on March 15, 1977.

The department is now drafting legislation in the light of the recommendations made by the committee, and the OMB is reviewing comments on such draft legislation. This legislation should be ready soon.

Mr. Chairman, I would like to submit for the record the Federal Interagency Committee's "Interim Report on Suggested Elements for Legislation," along with a copy of the Secretary's press release, which accompanied it.

Chairman THORNTON. Without objection, the material submitted will be made a part of the record.

[The material referred to follows]:

# HEW NEWS



U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

FOR RELEASE AT 1:00 P.M. EST  
Wednesday, March 16, 1977

National Institutes of Health  
Storm Whaley (301) 496-4461

New legislation is necessary to regulate the use and production of recombinant DNA molecules, according to a report transmitted today to the Secretary of Health, Education, and Welfare.

In accepting the report from the Federal Interagency Committee on Recombinant DNA Research, Secretary Joseph A. Califano, Jr., said that the Department will immediately begin drafting legislation in the light of the recommendations made by the Committee.

Califano noted that he had been closely monitoring the recombinant DNA issue since his confirmation and that he had been in continuous communication with Dr. Donald S. Fredrickson, M.D., Director, National Institutes of Health and Chairman of the Interagency Committee.

"I recognize that legislation in this area would represent an unusual regulation of activities affecting basic science but the potential hazards posed by recombinant DNA techniques warrant such a step at this time," Califano stated.

"But I believe that such a measure is necessary not just to safeguard the public but also to assure the continuation of basic research in this vital scientific area.

(more)

"We are not saying that research should be halted. We are urging that it should proceed under careful safeguards unless and until we have a better understanding of the risks and benefits posed by use of recombinant DNA techniques without government regulation," Califano said.

While agreeing with what he called the prudent recommendations of the Interagency Committee in this limited and most exceptional area, Califano reaffirmed his commitment to the principle of unfettered inquiry that applies in scientific research.

The Interagency Committee is composed of representatives of Federal departments and agencies that support and conduct recombinant DNA research or that have present or potential regulatory authority in this area.

The Interagency Committee recommended that any legislation should, among other things:

- place primary responsibility for the administration of the act on the Secretary of HEW;
- require any person engaging in such research, production, or use of DNA recombinant molecules to do so only at a facility licensed by the Secretary;
- require any person engaging in such activity to do so only after the project has been registered with the Secretary; and
- the Secretary should have authority to inspect facilities, make environmental measurements, and take other steps to ensure safety.

The Committee pointed out that this legislation would establish uniform standards for such activities throughout the Nation.



In addition, the Committee recommended that the NIH Guidelines for Research Involving Recombinant DNA Molecules become the national standard, with such modifications as the Secretary may consider necessary.

Califano stated that he asked HEW's General Counsel-Designate to work with Dr. Fredrickson, and the technical experts on the Interagency Committee, and to consult closely with the relevant Congressional committees in drafting legislation for clearance with the Office of Management and Budget and eventual submission to Congress, that would follow the Interagency Committee's recommendations.

## 215

## CONTENTS

CHAPTER	PAGE
I. Introduction . . . . .	1
II. Development of the NIH Guidelines on Recombinant DNA Research . . . . .	2
III. Federal Interagency Committee on Recombinant DNA Research . . . . .	3
IV. Subcommittee Review of Existing Legislation . . . . .	6
V. Suggested Elements for Legislation . . . . .	10
VI. Suggested Elements for Legislation: Committee Analysis	15
VII. Future Agenda . . . . .	20
APPENDICES	
I. Interagency Committee on Recombinant DNA Research . .	22
II. Subcommittee of the Interagency Committee on Recombinant DNA Research . . . . .	25
III. Regulation of Recombinant DNA Research in Laboratories	27
IV. Petition: Environmental Defense Fund and Natural Resources Defense Council . . . . .	40

INTERIM REPORT OF THE  
FEDERAL INTERAGENCY COMMITTEE ON RECOMBINANT DNA RESEARCH:  
SUGGESTED ELEMENTS FOR LEGISLATION  
March 15, 1977

I. Introduction

Recent scientific developments in genetics, particularly in the last four years, have culminated in the ability to join together genetic material from different sources in cell-free systems to form recombinant deoxyribonucleic acid (DNA) molecules. DNA is the material that determines hereditary characteristics of all known cells. Recombinant DNA research offers great promise for better understanding and improved treatment of human diseases. Medical advances through use of this technology include the opportunity to explore complicated diseases and the functioning of cells, to better understand a variety of hereditary defects, and possibly in the future, to create microorganisms useful in producing medically important compounds for the treatment and control of disease. Aside from the potential medical benefits, a variety of other applications in science and technology are envisioned. An example is the large-scale production of enzymes for industrial use. Potential benefits in agriculture include the enhancement of nitrogen fixation in certain plants and the biological control of pests, permitting increased food production.

There are risks in this new research area as well as anticipated benefits. A potential hazard, for example, is that the foreign DNA in a microorganism may alter it in unpredictable and undesirable ways. Should the altered microorganism escape from containment, it might infect human beings, animals, or plants, causing disease or modifying the environment.

# DEFINING NIH MANDATE 'NUMBER ONE QUESTION FOR US HERE,' SAYS NIH CHIEF; FREDRICKSON PREDICTS MORE RESPONSIBILITIES WILL BE ASSIGNED BY CONGRESS

*Full text of interview with "The Blue Sheet," but transcript not seen in advance or approved by NIH Director Fredrickson*

**Q** *Naturally, as a result of the change in the administration and your reappointment and your greatly increased off campus activity, there's a great deal of speculation all over the campus about what's going on and where it's all headed. . .*

**A** Well, I think that now that we have an asst. secty. for health — practically — some of the old lines will reform and it means we'll have to do less traveling. But probably we'll do more than we did in the past because the secty. likes to deal directly with his agency heads on certain matters and it makes for a better connection.

**Q** *Is it true, as far as you know, that there has been some actual cutback in the authority of the asst. secty. for health?*

**A** No. I really don't know that that's true or that that will be true. The only real change, of course, is the asst. secty. for health financing, or whatever the title is. So that does mean that there is another group.

**Q** *So the real change is the fact that Secty. Califano takes a personal, or direct, interest in the NIH as opposed to the former system where most of the communication was through the asst. secty. for health's office?*

**A** Yes. Compared with his predecessor, he takes a much more active role in dealing with agency heads and direct participation in lots of problems.

**Q** *If I could put what I've been hearing from managerial staff at NIH in its most extreme form, what they see coming down the road is a great reduction in the autonomy of the institutes — if not even an erasure of the disease-oriented institutes — and a reformation along functionally-oriented lines such as an Institute of Intramural Research, an Institute of Clinical Trials, an Institute of Basic Research, for example. Are these NIHers scaring themselves needlessly, are they talking about a direction that is real?*

**A** No. Not by any chance. I think that the only change that we'll see coming is perhaps — alas — some added new responsibilities for the institutes to carry out. Out particularly at the end of what we call the biomedical research continuum. And there's no probability — no likelihood whatsoever — that autonomy will decrease because there's no question in my mind that the manner in which the NIH goes along is really the best. It was good before and it will continue to be indispensable.

I think that the division of responsibilities across this continuum into disease-oriented, systems-oriented organizations is the only way to get the job done. I think that it's extremely important that you collect the expertise that there is on given sets of problems — maybe revolving around a major body or biological system — and that you give as much autonomy as you can, you provide maximum identity to the people involved because that's where they are going to do their best work and get the most satisfaction and that any other scheme of collectivization, or creating some sort of monolithic structure where all those things would disappear, would be extremely counterproductive.

**Q** *Isn't one of the reasons the NIH is going to be asked to take on the new responsibilities in technology transfer and elsewhere a belief on the part of Califano that the NIH can perform the functions, as opposed to other agencies?*



**A** The secty. hasn't indicated to me that he intends to change the mandate of the NIH in the slightest. Now, it's true that, primarily from the congressional side from time to time, we do hear suggestions of added responsibilities. And indeed the Congress has and will again this spring want to have another look at the mandates for research and what they mean. But the new Administration hasn't come in with a new plan for reorganizing the agencies to any considerable extent. They may want to do something of that sort. But clearly that's not the state in which they arrived and they'll need to do a lot more fact finding and analysis — and want to do that — before they'll make any such changes. But I would guess, I would say that there have been and will continue to be some suggestions from the Congress, some queries as to whether some of the deficits as they perceive them in the health care system cannot be better addressed and some of them by NIH. However, I think that's the subject for the spring. . . and the question of defining the mandate of NIH is a very major one, the number one question for us here. And that doesn't mean that we're trying to seek a radical redesign but to restate and understand what we think are appropriate boundaries.

**Q** *Can you state now how far down the road toward health care delivery you think the NIH can go, in terms of scientific opportunity, money and expertise?*

**A** I think that those questions arise from several sources. The most important is what is the perception of many people who care and who have responsibility for attempting to realign or correct or improve on what are seen as some of the deficiencies in the health care system. And the other side of the coin in addressing those questions is what has been the traditional role of the institutes, what's been the traditional role of biomedical research in relationship to the health delivery system. And then the third element is: are there any adjustments that need to be made that might do several things. One, help control the tremendous spiral of costs. Two, make sure that access to good medicine is as great as it can be for all the people. And the third is to make sure that the elements of medical practice that are available to everybody are as validated and safe and effective as they can be. I think that we've been approaching that from an examination of the traditional biomedical research system and the role that it plays in providing the new knowledge from which the new interventions come.

**Q** *We seemed to have arrived at a new era in research in which advances are so incremental they have to be validated in very expensive, longterm clinical trials. Have we arrived at some sort of scientific frontier beyond which we are probably not going to advance in large leaps?*

**A** Actually, there hasn't been any radical change in the scientific process with the exception that it's become somewhat more accelerated, that the emphasis on research in the past two decades has meant more and more discovery which has to be resynthesized into things that can be moved along the pathway toward practical application to man. The process remains basically the same, but the need for applications and the opportunity for applications, and the need for validation has dramatically increased because we know so much more. You know it's never been true — or been very rarely the case — that this lone individual in the laboratory has made a single discovery which — Eureka! — could be immediately applied to maximum benefit for the health of a lot of people.

**Q** *Hasn't the image been one of individual investigators standing on the shoulders of other individuals, or extremely small groups, and then coming up perhaps serendipitously with a one-shot, silver bullet?*

**A** Well, that's still the nature of the process, but remember it's much more of a mosaic than a masterpiece by a single individual. And it takes a lot of time and tremendous amount of work. Serendipidity is important, but perseverance and reasonable planning are far more important and sustained, stable support for those activities.

**Q** *Like the space shot?*

[More]



**A** No. The space shot example is a bad one for biomedical research. It's an engineering project. It's based on the knowledge that if you put all the elements together you can get to where you want to go. But that isn't true of most research in matters of biology and health and disease. There are very few space shots that can be engineered in this particular area.

**Q** *Have we then given up the dream of curing cancer, for example. Is the advent of the technology-transfer, clinical-trials era a confession that the dream was unrealistic to begin with, a confession of defeat?*

**A** Oh, no. It's not unrealistic to dream of cures for almost anything that man suffers from. It's more realistic, however, to both work for and expect the real achievements will be prevention in the first place. Because it's much easier to prevent many things than to correct them. An example is a comparison between replacing a damaged heart and preventing the damage in the first instance.

**Q** *There are people, including scientists, who believe that a whole new orientation toward prevention is a dream as equally grand as cure and one that is achievable. . . people who would put virtually all the effort into prevention and let the care of disease take a back seat.*

**A** To be quite honest with you I don't agree with that point of view. The tradition has been prevention. Everybody has been looking for those ways that could eradicate disease, but it is a fact that we don't have enough knowledge. And while we're waiting for that — and certainly attempting to make sure that we use every opportunity to get the knowledge that we need until the time that it comes together in the form of a preventive action — we can't leave neglected those that now have certain problems because it is in the natural march of science that alleviation, some technological correction or assistance, has been more feasible than the preventive stroke itself.

**Q** *Is there a philosophical split between traditional medical practice and the desire to achieve a healthy society? Wouldn't a doctor rather have you come in with your bleeding body, wouldn't he be more interested?*

**A** No. I really don't think there's any tension within the medical community to prevent prevention. Not at all.

**Q** *Then you see people dashing into epidemiology when and if the opportunity exists?*

**A** The problem there is not that people don't want to go into disciplines that are naturally more related to prevention than to cure. Not at all. It's just that those disciplines are by nature much less exciting in immediate terms and have far less in the way of an immediate reward or particularly individual reward than do many other fields that you doubtless have in mind. I think that one is dealing in research with the human ego and the need for self-gratification which is gained from not only a disciplined life of hard work and anticipation but occasionally a discovery. And one that has relevance and hopefully, utility in one's own time.

**Q** *You don't think there are two mentalities then, each equally admirable, but different?*

**A** No. I don't think that's at all true. And I think this is particularly gainsaid by a notable relevance kick among the very best in science today. People who have made striking achievements in cell biology want to apply those techniques and what they know to very practical problems. An example is many people who have worked on cell structure, organelles, functions of single reactions who are very keen to apply those to the field of tropical medicine or other areas where they may have an enormous impact, or potentially have an enormous impact. I think that biomedical science is a very humane discipline. I think you could even put it in the most callow terms: every scientist would like his discovery to be relevant and to mean something to people even if it only meant that because



it did he would feel that his work was that much more important. I don't think there's an ivory tower in biology.

**Q** *How would you respond to a recent proposal that the whole of the clinical trials effort be lodged in one institute — new or expanded?*

**A** There isn't anything very practical about that suggestion because the content of clinical trials is always still subspecialty oriented. You could no more imagine creating a separate group of people who could at the same time manage large-scale dietary trials and their effects on blood lipids, on the one hand, and the effect of laser coagulation of retinal arterial lesions, on the other. There's an inescapable requirement for subspecialty expertise in the execution and interpretation of all these clinical trials and that's another reason why we can never do away with the institute structure. Because that's where the expertise lies. There are all-purpose specialists who are related to the process of clinical trials, of course. There are biometricians, statisticians, epidemiologists and clinicians. But they would have to be supplemented by, almost always led by, specialists who are most *au courant* with the specific problems that are being dealt with. Because they are the ones who will understand best the requirements of the protocol and who know what to anticipate in the way of benefits and bad side effects and so forth. You can't have a single unit that does all of the validation.

**Q** *If and when we have a natl. health insurance system, will clinical trials be introduced as a regular component of the health care system as they are in England for example, or are they going to continue to be a separate clinical-research-type activity?*

**A** They will be some part of that because clinical trials now of any order of magnitude are carried out in our existing health care system.

**Q** *Because of the advent of Medicaid and Medicare?*

**A** No. Not particularly because of that. They'd be carried out in any kind of health care system. But, you know, when you look at clinical trials that are conducted abroad you are often dismayed by the difference between costs that seem to be present there as opposed to much higher costs here. Now, most of these cost differences arise because in some countries you don't have to amortize the bed costs — patient care costs — because they are taken out automatically or cared for by some single natl. system. The second reason is that personnel costs are simply so much higher in this country. So clinical trials will continue to be much more expensive here.

**Q** *Do you see any major changes in clinical trials methodology coming along, so that trials could be telescoped? The whole method of validating therapies carried out more cheaply and quickly?*

**A** No. That's not the way it's going to go. We're going to see a steady and continuing improvement in our ability to devise experiments that both ask good questions and lead to meaningful answers. But there are many aspects of these trials that cannot be foreshortened because the endpoint simply requires a certain amount of time. I think our methodology has dramatically improved in the last ten or fifteen years and it's certainly going to continue to do that as we get more experience. There will be changes in the conduct of the trials in many matters of style and process, but the fundamental questions may still take a lot of time and a lot of people to answer. Particularly because these trials are beginning to engage questions of chronic disease, more and more. Whereas it might take only five patients with meningitis to determine the effect of an antibiotic that would be dramatic — unquestioned — and where you wouldn't have any difficulty determining a p value, when you're looking at the alleviation of pain in arthritis, when you're looking at something that can prevent the slow development of atherosclerosis, the problem is completely different in terms of inputs. On the other hand, you can count on science developing greater sensitivity of its methods and there will be other

inputs that will be developed that will be cheaper and faster and so forth. So as basic science continues to roll out useful knowledge, so will that knowledge be applicable to clinical trials.

- Q** *Don't the subjects perceive these large-scale trials as service?*
- A** There's an inevitable service delivery component to many clinical trials because one is dealing with people who are ill and it's grave responsibility to assure that the best available care isn't being neglected.
- Q** *So even if they aren't getting what you hope will turn out to be the preferred treatment, they are getting the best treatment available, minus the experimental element?*
- A** That's a very important moral and ethical issue that must be dealt with in setting up any clinical trial.
- Q** *You never give one group nothing.*
- A** Well, that's not true in the sense that if you don't know whether giving treatment is better than nothing, it frequently is decided to randomize the patients and give one control group no treatment and the other group the treatment. Now, the only moral basis on which you can proceed is to be sure that there is general agreement that we really don't know. If we are sure, the consensus is clear that we do know, then there's no basis whatsoever for a trial. What we do centrally at NIH in the Office of the Director is to have a clinical trials coordinating cmte. which includes representatives from all the institutes. And this group is charged with becoming aware of all the clinical trials, with offering useful critiques of those trials, with being sure that we derive every lesson we can from them about how we might do the next trial better. It also allows us to keep a running census of exactly what questions are being asked, how they are being asked and how well we are getting the answers. We'll have another clinical trials inventory for this year, we're sharpening it now.
- Q** *Why should the NIH be responsible for the function of validation?*
- A** Well, the NIH isn't necessarily responsible for all validation. We haven't agreed — any of us — that that is necessarily true or even possible for the agency. It's clear that we must engage in a great deal of these validation exercises, particularly where they relate to new interventions because these new interventions inevitably arise out of biomedical research. Since our role in sponsoring, conducting and supporting research is very large, we can't escape that responsibility. Nor do I think we should, wherever there is an important scientific question to be answered by the techniques in which we are — we and the community we support, which is very important to underline — the best source of that expertise. Very careful choices will have to be made. There are some questions of validation that quite probably will not be appropriate for this agency to attempt to answer.
- Q** *Such as?*
- A** We'd not be the experts in answering a question such as "would it be better if we adopted a universal medical record?"
- Q** *You mean that's something for the Center for Health Statistics, or whatever?*
- A** I think that's the kind of question that other agencies are better equipped, or should become better equipped, to deal with. They are questions that require a far greater access to the practicing community than we have. We deal primarily with the biomedical research community, the academic medical centers, and they might not be the best at all to answer these kinds of questions. There are other kinds of field trials and applications where one really needs to get into the community and have longstanding arrangements and connections with those community enterprises that we don't have.



**Q** *For the questions that are appropriate to NIH, is there going to be new money for what seems to be a new venture?*

**A** It's not new. It's an extension of what we've been doing for many, many years here, but there's an increasing need for it and they are getting increasingly costly. And we've spoken frankly with the Congress — both in the House and the Senate — and told them we'd have to choose carefully which problems we ought to address. Choosing them has several elements: the need and the opportunity to find out useful answers — that can be very important — and the ability to support and pay for such trials. Now, as these kinds of activities increase, it's very clear to all concerned that we'll have to amortize those costs. Perhaps there will be some way we can do that through natl. health insurance, or there will have to be other added funds to make it possible. Because everybody recognizes that at the same time we engage in this we have to very carefully tend to the less practical, less differentiated, very important so-called fundamental biological research from which some of the most important answers are going to come. One can argue strongly for separating all those activities into two kinds, let somebody worry about the basic and somebody else worry about the clinical, but in practical terms it doesn't work that way because at the level of development of turning knowledge into the practical you often need the same kinds of people involved. It's in many ways much easier for an agency like NIH to keep its eye on both sides, both ends of the continuum and to make reasoned arguments for maintaining the appropriate balance that must exist.

**Q** *How much basic research do you have to have to preserve a critical mass?*

**A** There isn't any absolutely strict figure because no one knows how to develop such criteria, but there are other more or less direct criteria. One is to be very carefully attentive of the number of research project grants that are fundable every year because they represent the best index that we have of the investigator-initiated, usually less differentiated research, that is basic. We need to know the capacity of the several institutes to fund such grant applications when they are approved, we watch carefully their ability to pay. We're also very much interested in what percentage of those new applications represent new people, the entry of new principal investigators into the system to be sure that we haven't squeezed out that essential ingredient which is renewal. And we watch that as our most careful index and we try to relate it to more aggregated support like program projects, center developments, and we compare those to other large-scale clinical trials and applications research.

**Q** *There has been a falling off of the level of funding of approved grant applications; in some cases it's been dramatic. Is this a temporary phenomenon — a result of the upheavals of the early 70s, or do you think you'll have to settle for a 30% standard?*

**A** Well, now you ask me a question that none of us can answer. What will be the continued course of Congressional and Administration support? Yes, some institutes have had alarming falls in their purchasing power over the last five years; some of them have lost in absolute purchasing power — we know that. Several of the institutes have either maintained their fraction of the total or increased it. And it is part of the continuing responsibility that I think we have for addressing every point along the spectrum to see that we don't let certain areas sag, to see that the less visible are not overtaken by the more visible initiatives that arise often not from within the scientific community but from outside.

**Q** *Do you see yourself becoming more visible in an effort to try to maintain a proper balance? Are you going to be increasing your contacts with Congress throughout the fiscal year? Do you have, in effect, a new job?*

**A** Well, the Administration — the high levels of the Administration — and the Congress are not going to yield any of the prerogatives, and I'm not sure they should. If you look at the budget process, the Office of the Director, NIH is the one place where all of the ambitions and plans and

## FREDRICKSON ON THE NIH FUTURE

opportunities that each of the institutes feels it has for changing the direction of research or for increasing or decreasing its emphasis are given what we intend to be a very objective and fair scrubbing. And this is the last line of technical review and so we try to make our estimates as carefully — to represent the best advice — as we can to the Administration.

**Q** *Do you see the gap between the institutes' request and the administration budget (as reflected in the Ford/Carter budget) disappearing?*

**A** Remember that the Administration sets a budget and they decide how much they want to spend and down through all those branches and twigs decisions must be made and priorities must be made that will adjust to the final figure, and I don't see that that process will ever change.

**Q** *What's on the immediate agenda; What issues or topics of the level of intensity of DNA, for example?*

**A** Well, the [Senate Health] Subcmte. oversight hearings where we'll deal with the issue of the mandate. No date has yet been set for the start of the hearings. Then there's the review of the President's [Biomedical Research] Panel and questions of long-range authorization. Peer review is another. The report from the Peer Review Study Group has been farmed out to the institutes for their comments. Then there are six cross-cutting, trans-NIH issues which will appear in the Forward Plan and will be the subject of study throughout the spring. These are nutrition, diabetes, cystic fibrosis, genetic diseases, arthritis and epidemiology. Another trans-NIH subject will be training. And finally, the big modernization move on the new Ambulatory Care Research Center, where construction is scheduled to begin May 1.

## STATE OR REGIONAL CAPS ON HOSPITAL CAPITAL OUTLAY PUSHED BY BHRD; RATE REGULATION, PLANNING MUST BE INTEGRATED OR NEITHER WILL WORK

A Bureau of Health Planning and Resources Development staff paper developed at the request of planning chief Harry Cain recommends a greatly increased integration of planning and ratesetting by the federal govt.

Among the recommendations to dept. and congressional leaders in the preliminary document are specific limits on capital expenditures and/or annual operating expense increases by state and region. Allocation of capital expenses by geographic area is reportedly gaining favor in White House and congressional circles and may be included in the Administration's long-term cost control program.

**"Without an aggressive planning program, rate regulation decisions can, inadvertently, 'freeze' the existing system, vitiating efforts to improve it," the paper says. "In turn, without rate regulation or ceilings on expenditures, tough planning decisions are less likely to be made and rate regulation can help to implement the plans."**

Natl. guidelines would set a natl. goal to limit expenditures in concert with state guidelines "to allow appropriate variances from natl. goals and to identify state priorities." Areawide guidelines would "identify major plan priorities within resource ceilings."

"One approach would be to require that depreciation be funded, and that the funded depreciation be pooled for future use by the community as a whole," the paper notes. "Or, each year hospitals could be permitted to grow only by some set amount. Each may be allowed to 'reserve' its own depreciation and capital funds for major changes needed less frequently."



## RESEARCH AND THE POLITICAL PROCESS

My topic for tonight, as printed in the program, is "The NIH Today: a Status Report." That, I believe, is the usual topic for the NIH segment of these meetings. Well, to put it most succinctly, the status of NIH is good. Its principal tasks, in historical order, are to conduct research in its own facilities and to provide support for research conducted elsewhere--and research in both areas is flourishing. I think you will agree that NIH's intramural community has earned recognition as one of the major centers for biomedical research--the reception accorded papers presented by NIH scientists at these meetings attests to that and any misgivings a Director of NIH might have are periodically dispelled by the award of a professional honor, occasionally even a Nobel Prize, to some scientist he has seen pottering about in one of the labs for a number of years. There is no need for the Director of NIH to have misgivings about the success of the extramural programs: this country has for some years been the acknowledged leader in biomedical research and, as NIH provides the funds for two-thirds of this research and is the major source of support for health research in academic and non-profit institutions, the extramural programs must be on the right track. Of course we have administrative and operational problems but they are similar to those that inevitably beset any large and multi-faceted organization. In short, I believe that NIH is in sound and sturdy ship that has traveled far and has much farther yet to go.

My concern is to keep the ship on a safe and steady course through whatever shoals and bad weather may lie ahead. Rather than talk to you about where we have been--or about where we are--I should like to discuss

with you where we may, or should, be going. This involves policy questions many of which will necessarily be decided in the political arena. The topic I would, therefore, choose for our discussion tonight is "Research and the Political Process." The principal points which we should consider can then be grouped under three headings:

- ... the competition for resources;
- ... peer review under the 'sunshine' laws; and
- ... the public governance of research practices.

I am calling this a discussion because I want us to engage in a dialogue on these and other policy issues that will come to mind as we ramble along together. I am sure that all of you are, in one way or another, involved in research; I am not so sure that all of you are aware that you are also involved in the political process. Some of you, no doubt, do take an active part in the political process but those of you who do not should remember that passivity on political questions weighs as a political decision: in the political process, as in research, negative results--or inertness--are also taken into account. As the Director of a federal research agency, I am involved in both the research and the political processes. Your comments and your questions will be of much practical interest and immensely useful to me.



The Competition for Resources

The most obvious example of the impact of the political process on medical research is the annual exercise that determines the appropriations for the National Institutes of Health. It is a simple fact that the tremendous expansion of biomedical research in this country during the past 20 years--and <sup>the</sup> professional leadership attained by American scientists during this period--are primarily due to two politicians who, in 1956, were the chairmen of the House and Senate Subcommittees that dealt with the NIH appropriations. They became convinced--and some of the credit must go to those who convinced them--that biomedical research in the U.S. was lagging; that it needed to be greatly expanded; and that Federal support, through the NIH grant programs, was the most effective way of stimulating such an expansion. Their modus operandi was, on the surface at least, quite simple: Representative Fogarty and his Subcommittee would recommend, and the House would vote, a substantial increase over the amount recommended in the President's budget; Senator Hill and his Subcommittee would then accept the House increases and recommend a still greater increase for which the Senate would duly vote; in the subsequent House-Senate conference, to reconcile differences in the two bills, Rep. Fogarty and his colleagues would agree to half of the Senate increase over the House figure and the resultant amount would become the NIH appropriation. In the face of the large increases thus provided, the Administration, understandably, would hold the next year's budget request for NIH to the level of the current year's appropriation at which Messrs. Fogarty and Hill would loudly express their dismay--and then repeat the process. By this means,

the funds available for biomedical research through NIH were raised, for seven consecutive years (FY 1957 through FY 1963), by an average of 30 percent per year--or from \$98 million in 1956 to \$930 million in 1963.

According to NIH mythology, these seven fat years, following the Biblical precedent, were followed by seven lean years--but this is, indeed, a myth. An almost ten-fold increase having been achieved, the pace inevitably slowed--if it had not, the NIH appropriation would now be \$84 billion! The pattern established by Messrs. Fogarty and Hill has, however, been continued by their successors: Representative Flood and Senator Magnuson. By 1970, the NIH appropriation had risen to \$1.5 billion--a 61% increase in 7 years; for 1977 it is \$2.5 billion--a 66% increase in 7 years. It is true, of course, that about half of these increases--perhaps a little more--are offset by inflation but the rest represents expansion of program, virtually all of which is extramural.

You may well ask--as, indeed, I am asking--will this pattern continue? Unfortunately, the Washington political process is as predictable as the Washington weather and it is now further complicated by the existence of two new high-pressure areas: one on Capitol Hill and the other in the White House.

In 1975 Congress passed a new Budget Act, which came into full effect for <sup>the current</sup> ~~the~~ fiscal year, designed to forestall what Congress regarded, with some justification, as high-handed White House actions in recent years. This Act proscribes the withholding of appropriated funds by the President--whose authority for doing so was always tenuous and had rarely been used before the advent of President Nixon and was eventually denied by the Courts--and sets up a system under which the President can ask for

a rescission of funds he regards as excessive or unnecessary but cannot carry out the rescission unless both houses of Congress agree within 45 days. The Congress was also concerned about the increasing tendency in the White House to veto appropriation bills--as a result of vetos there were no NIH appropriations in 1973 and we continued to function under stop-gap legislation known as a "Continuing Resolution." The President clearly has constitutional authority for such vetos and they are difficult to override because that requires a two-thirds vote and puts a strain on party loyalty. The best way to forestall a veto is to send the President a bill that is reasonable and reasoned. To this end, the new Act set up a Congressional Budget Committee, with a professional staff, which prepares a budget that is independent of the President's budget and goes into considerably less detail. Its gross totals, though subject to modification at stated intervals during the Congressional budget process, are meant to be binding on the appropriations committees and to severely limit their ability to vote large increases without compensating decreases elsewhere. It is too early to say how this will work out or how NIH will be affected. The process will clearly have the restraining effect that is intended only if the Budget Committee succeeds in bringing the Appropriations Committees to heel--which is not an easy but not necessarily an impossible task.

The other factor that may inhibit Congressional largess is that the Democratic leadership must now react to<sup>a</sup>/budget proposal made by a Democratic President. There may well be political advantages, and probably some personal satisfaction, for a member of Congress to fly in the face of a

President from the other party, but the risks are obviously greater if he is on the same team. The President's aim of balancing the budget by 1980 can not be achieved without Congressional cooperation and considerably more restraint than has been exhibited in the past--even under Democratic Presidents. It remains to be seen whether party loyalty will now prove stronger than the tension that the Constitution has built into the relationship between the President and the Congress by ignoring the President's role as leader of his party and putting him in the adversarial position of being the head of the Executive Branch co-equal with the Congress. From the narrow view of NIH, the Democratically-controlled Appropriations Committees during the Kennedy and Johnson administrations were more notable for their independence than for their loyalty to the President and his desiderata.

If it is unclear how NIH will fare in the inevitable tug-of-war between the Congress and the President, it is also unclear how NIH will fare in the intra-administration skirmishes that arise in the preparation of the President's budget. The contestants here are the Office of Management and Budget, a part of the President's Executive Office, which must adjudicate the competing claims of all the government departments; the Office of the Secretary, which must allocate the amount sanctioned by the OMB to the health, education, and welfare components of the Department; and the Office of the Assistant Secretary for Health who must divide the health share of the funds to the several health agencies, of which NIH is one. Naturally, there are not enough funds to satisfy all claimants at any



stage of this process. The allotments do not pass from stage to stage with no strings attached--increases or decreases may be imposed for specific programs or activities at any stage. For NIH, there is the further complication that under the special legislation for the Cancer Program, launched in 1972, the National Cancer Institute theoretically submits its budget request directly to the President, with the result that the OMB allowance for NCI may not be altered.

In the past, most of NIH's budget difficulties have been with the budget examiners at OMB who had strong views

...about General Research Support Grants which were awarded to institutions according to a formula based on the amount of research grant funds they received and were regarded by OMB as a slush fund, and

...about the research training programs which they regarded as an unwarranted means for building up <sup>future</sup> ~~the~~ demands for research grant support.

Previous Secretaries of HEW repeatedly prevailed on OMB to provide funds for training, though on a reduced scale. They have usually been increased by the Congress. Training funds are included in the FY 1978 budget that President Ford submitted to Congress but with new awards limited to postdoctoral fellowships--new predoctoral fellowships and new block grants to institutions are excluded. This item was not included in the changes proposed by President Carter which, because of the short time available for revising the budget, were necessarily kept to a minimum. General Research Support Grants--now renamed Biomedical Research Support Grants and awarded under somewhat different rules--have not appeared in a

President's budget for several years but have always been restored by the Congress. Secretary Califano supported NIH's plea to have these funds restored in the FY 1978 budget but OMB did not do so. It is not clear whether this reflects the new administration's policy or an unpremeditated hold-over of previous policy by the budget examiners who presumably made the decision.

The policies of this administration, as they affect NIH, will not become clear until the process of putting the FY 1979 budget together is underway. But it does not require any special acumen to predict that major or across-the-board increases should not be expected. The fiscal commitments and economic pressures that have bounded the budget process in recent years will not have significantly altered and it can not be convincingly argued that an investment of \$2.5 billion is inadequate to support a first-class and vigorous biomedical research effort.

There remains one further enigma in the annual competition for resources and that is the effect of what is called zero-base budgeting. Under the traditional system, the NIH budget--like that of other agencies--was largely determined by the projected cost of continuing existing activities, making adjustments here and there for activities that were to be expanded or contracted. There was, in fact, very little scope for making changes at the various levels of decision which I have described. In fact, so-called mandatories and what at NIH are called moral commitments absorbed the bulk of the funds allotted to every stage. The principle of zero-base budgeting is that no previous allotment of funds is automatically carried forward and that all activities be judged afresh, on their individual merits, in competition with all other activities. In its most

extreme form, one would have to decide how one would fund NIH if one were starting de novo. There would, theoretically, be no floor and no ceiling for budget estimates. In practice, of course, the decision will be that most existing activities are proper and worthy of inclusion in the new budget structure. But their continued existence will have to be justified--and convincingly enough to withstand the competition of other demands for funds at each successive rung on the budget ladder.

The effect and, indeed, the purpose of zero-base budgeting is to focus attention on the quality, effectiveness, and appropriateness of every activity. And that is not a bad approach to the stewardship of public funds or the management of research. It is, in fact, an extrapolation and broader application of the principles that underline the NIH peer review system for grant applications.

That brings me to my next topic, so it may be well to stop here for a discussion on the competition for resources and related questions that occur to you.

Peer Review Under the 'Sunshine' Laws

When, in the post-war reorganization of Federal support for biomedical research, the existing grants-program of the war-time Office of Scientific Research and Development was turned over to NIH--which was at that time essentially an intramural research organization--a system had to be devised for assessing the merits of grant applications as objectively as possible. To this end, a two-tiered peer review system was set up consisting of discipline-oriented Study Sections, wholly comprised of scientists, to assess the scientific merits of a proposal, and mission-oriented Advisory Councils, comprised mainly of members of the relevant professions but including some lay members, to judge the importance of the proposed project to the purposes of NIH. There was precedent for the Study Sections in the Scientific Advisory Board of non-governmental scientists established by Congress in 1902 to advise the Surgeon-General on the administration of NIH's predecessor, the PHS Hygienic Laboratory. Peer review was also specifically endorsed by a scientific review board appointed by the President in 1947--the year in which the growth of the NIH grants-programs began. The Advisory Councils were sanctioned, indeed required, by the legislation under which the various Institutes were created.

The system has worked well and during its first 10 years evoked little criticism and was subjected to no outside scrutiny. In 1958 a group of consultants to the Secretary of HEW projected that national support for medical research would expand to \$1 billion a year by 1970 and they predicted that the NIH extramural program would evolve towards larger grants for more broadly defined research purposes and that this would require changes in



the traditional Study Section system. In the event, the first two of these predictions have been borne out but without producing a need for major or substantive changes in the peer review system. During the ensuing two decades, more than a dozen reports have been issued by Presidential, Congressional and non-Federal committees and commissions that have reviewed or commented on the NIH peer review system. Without exception, they have endorsed the principles on which it is based and have praised its effectiveness--but not, of course, without criticism of various aspects of the system and recommendations for strengthening or further improving it. Some of these criticisms and recommendations concerned administrative or operational matters such as the excessive work-load for Study Sector members, their need for more supporting staff, briefing, etc., which affect the comfort rather than the comport of the system.

It would be pleasant to dwell on the many tributes to the system, and to the NIH extramural program built upon it, that recur in these documents--from the Bo Jones report for the Senate Appropriations Committee in 1960 to that of the President's Biomedical Research Panel in 1976--but it is more appropriate to our present purpose to note the points raised, either in criticism or disavowal, that bear on the integrity of the system and thus have at least potential political relevance. In the main, they simply reflect various aspects of the dilemma--noted 30 years ago in a report to the President by his Scientific Research Board--that review must be conducted by experts from leading institutions to ensure the best possible advice and that majority of the proposal they must evaluate come from the staff or graduates of these same institutions. This is, of course, just another way of stating the inescapable truism that in a system of peer review, the reviewers and the reviewed are members of the same peer group.

Many outside observers are uncomfortable with that arrangement even when they recognize--as most of them do--that the system has been remarkably effective in maintaining the quality of grant-supported research during a period of rapid expansion. There is concern about conflict of interest, about the reappointment of distinguished people to other advisory committees, about an alleged buddy system, about favoritism to investigators at distinguished institutions so that the rich get richer, about the secrecy of the deliberations, and about the finality of a system that provides for no intercession and no appeal.

Although there has been no real challenge to the system, as such, there is a degree of validity in some of the concern and sufficient discomfiture to warrant a review of its management and operation. Such a review was launched last year <sup>by</sup> an in-house Study Team consisting of scientists and administrators, under the chairmanship of Dr. Ruth Kirschstein, the Director of the National Institute of General Medical Sciences. The first phase of its study included three public hearings--in Washington, in San Francisco and here in Chicago--many letters from scientists and the general public, and a survey of NIH advisory. The report on this phase, which has just been submitted to me, contains a thoughtful review and analysis of the criticisms and makes more than 50 recommendations many of which, of course, deal with nuts-and-bolts problems that can, for the most part, be easily corrected. But some represent a marked departure from our current peer review procedures and will require careful evaluation of their potential implications. The following are among the major recommendations of the Study Team:

... A formal NIH Grants Peer Review Appeals System should be established, including an ombudsman to be appointed by the NIH Director.

... Upcoming vacancies on Initial Review Groups should be announced periodically.

... The NIH Director should be delegated the authority to establish or discontinue Initial Review Groups.

... The Assistant Secretary for Health, HEW, should be delegated the authority for selection and appointment of members of Advisory Councils.

... Portions of the meetings of advisory groups which involve the review of grant applications should continue to be closed to the public (including those submitting applications).

... The principal investigator should be sent a copy of the summary statement associated with his or her application as soon as possible after the grant application is reviewed by the National Advisory Council or Board.

... The workload of the Initial Review Groups should be limited to help ensure a high quality of review.

The Study Team also made recommendations concerning a variety of other key issues. These include identification and special consideration of unorthodox research approaches, conflict of interest procedures applicable to review group members, increased use of business management consultants as an adjunct to scientific review, and continuing studies of procedures designed to improve the grants peer review system.

Some of these recommendations are designed to cope with the so-called 'Sunshine' Laws which, as they now stand, pose a greater threat to the

integrity and effectiveness of peer review than the criticisms and concerns that have from time to time been expressed. There are four Acts that impinge on the peer review system.

... The Freedom of Information Act, as amended in 1974, requires agencies to make available to the public, for inspection and copying, any requested Government records: only three of the exemptions included in the Act apply to peer review:

- trade secrets and commercial or financial information that is privileged or confidential;
- certain inter-agency and intra-agency memoranda; and
- personnel and medical files whose disclosure would be an unwarranted invasion of private property.

The courts have ruled, in a case brought against NIH under this Act, that initial grant applicants, if funded, and continuation, supplemental and renewal applications, whether funded or not, and interim progress reports must be made available to anyone who wants them--except that information that would adversely affect patent rights or confidential financial information about the applicant may be deleted.

... The Privacy Act is designed to protect people from the collection and use of data about them by the Government, without their consent, and gives them access to such data as has been collected. This has the effect of making grant and fellowship review documents, including site visit reports, available to the grant or fellowship applicant.

... The Federal Advisory Committee Act is designed to ensure public knowledge of and access to meetings of Governmental Advisory Groups.



... The Government in the Sunshine Act sets forth the circumstances under which NIH may close advisory group meetings to the public. The exemptions are similar to those in the Freedom of Information Act but with an additional exemption for meetings that disclose information, the premature disclosure of which would be likely to significantly frustrate implementation of a proposed agency action.

This is too brief a summary to convey fully the complications of interpreting the application of these laws to the NIH dual review process. Their ultimate effect could be--and, indeed, their intent clearly is--to remove virtually all confidentiality from a process that relies heavily on assurances of confidentiality: on the part of a grant applicant that his research plans will not be revealed to potential rivals, on the part of the reviewers that their candor will not sour their professional and personnel relations with colleagues, on the part of an investigator that his research results will not be prematurely disclosed, and on the part of the public that published research results have been properly validated.

The legal experts have not yet fully resolved how the requirements and the intent of these laws, which have widespread public support and are clearly designed to promote the public good, can be met while also maintaining the essential features of peer review that ensure its objectivity, its candor and its thoroughness. It is, in fact, quite likely that the dilemma cannot be resolved without further legislation but there is a genuine reluctance in Congress to weaken or dim the sunshine laws or provide special shade for a particular agency.

Preoccupation with the problems resulting from these laws should not, however, blind us to their good effects. There are many areas of research in which it is becoming increasingly important to blend purely scientific or technical assessment with social, economic and ethical value judgments that lie well within the domain of the general public. The scientific community has an obligation--and must, for its own protection--take steps to bring the public within the ambit of its debates and decision-making processes.

This brings me to my third topic, the public governance of science. So we might stop here for a discussion of peer review and confidentiality problems.

### Public Governance of Research Practices

The increase in the power of science to create real or imaginable threats to man and his planet is seriously troubling not only to the public but to scientists themselves. The sobering realization that many of science's triumphs bear overtones of impending disaster began in atomic physics some 30 years ago but has now been extended by the duplicity of such supposedly beneficial agents as DDT and Kepone and the speculative hazards inherent in the otherwise promising advances in research on the mechanisms of genetics. Our political and legal institutions have responded to the ascending power of science with ever more complex restraints. While science, to date, has survived regulation on radiation sources, human experimentation, and laboratory hazards and has, indeed, generally benefited from a reasonable and reassuring set of common standards, the proliferation of Federal regulations, and of new agencies to enforce them, is now viewed by many as threatening individual initiative and other American traditions.

The public governance of science is seen by some scientists as running counter to the sovereignty of science and as a denial of their intellectual freedom. But this view denies the complexity of modern society. Science has always been part of the intellectual fabric that also embodies political thought and cultural traditions. It must operate in accordance with the law and cannot be above the law. As Arnold Toynbee has pointed out, the nemesis of creative institutions is the temptation to idolize themselves to the point of missing voluntary accommodation to altered realities.

We are in a major transitional phase. Biomedical research is passing from an extended period of relative privacy and autonomy to engagement with new ethical, legal, and social imperatives under concerned public scrutiny. But, as we move fitfully toward greater public governance of science, it is vital, for the sake of the public good, that we find the proper limits to this shift. Total faith in external regulation is a dangerous illusion. Public control of science is critically dependent upon a complementary self-regulation by scientists and their institutions. Responsibility for standards-setting, a necessary antecedent to any regulatory process, must necessarily remain largely in the hands of technical experts because the subject matter is complex and in constant flux. The public must not be deluded that technical issues--such as what is excellent and safe and what is not--are better first addressed by laymen in courts, commissions, or hearing rooms. Nor can the real control of scientific practices be exercised by commissions of mixed representation, by inspectors of an external agency, or even by scientific peers at a distance. It is "proximal governance"--carried out between scientists and their home institutions--upon which society must primarily depend. This is the level at which the capabilities, responsibility, and the observance of technical standards and moral and ethical principles in the conduct of research are best monitored. Scientists must be fully accountable to their peers who, acting collectively, must take responsibility for all practices within their institution that bear upon the interests of the surrounding community and society at large.

NIH has translated certain mandates for governance to the proximal level by requiring the formation of review boards to oversee human



experimentation, animal care, and now genetic recombination experiments. These, or similar bodies, may soon have to oversee other hazardous laboratory work, including fulfillment of a need to convey appropriate information to the surrounding community. These responsibilities are meaningful and inescapable adjustments to the rising concern for public governance of science.

As public governance of science continues to grow, we must be careful that we do not go beyond the critical limits to external control of the scientific process lest the system falter and its promise fail. An extravagant use of government rules and regulations is no less threatening than an extravagant degree of scientific autonomy. There is serious danger in any intrusion upon the processes of inquiry which is not clearly required for public safety. Legislation cannot enhance but may seriously impede the human and intellectual qualities necessary for successful research. The creative engines can be fueled by governments, but they cannot be ignited by them. The unknown cannot be programmed, nor discovery scheduled. The process must be self-directed, and scientists must, perforce, remain the judges of what is scientifically valid. There are invaluable elements of the scientific method that cannot be sacrificed to uncomprehending "reform." Conflict over the governance of science must be resolved by a deliberate and sensitive accommodation between the scientists' objective knowledge and the public's value judgments.

The scientific community, for its part, must tolerate and understand the nature of our political and legal institutions that govern science. It

must anticipate public needs or fears, learn better to explain, and take more responsibility for its technology. Scientific advice must be freely, and more understandably, available to governments which must receive from the scientific community the full measure of cooperation upon which they desperately depend. And there must be mechanisms within the scientific community that will, credibly and openly, give fair consideration of non-technical concerns and values.

The public, for its part, must understand the perishability of the capital, both human and physical, assembled by the nation's heavy investment in research. It must understand the organic nature of scientific processes and the ease with which they can be stifled by inflexible regulation or rigid mandates for discovery.

Effective governance that ~~will~~ protect both the welfare of the public and the freedom of science depends on adequate communication and willing accommodation. There is heartening evidence that society, whose right to know is incontestable and whose need to understand is real, is intent upon achieving the essential communication. It is up to the scientific community to respond. The seemingly adversarial process can be mutually beneficial. Man's genius for discovery is matched by his art in compromise. As Felix Frankfurter wrote, what ties people in friendship is not an identity of opinions but a harmony of aims.

RECOMBINANT DNA REGULATION ACT, 1977

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HEARING  
BEFORE THE  
SUBCOMMITTEE ON  
HEALTH AND SCIENTIFIC RESEARCH  
OF THE  
COMMITTEE ON HUMAN RESOURCES  
UNITED STATES SENATE  
NINETY-FIFTH CONGRESS  
FIRST SESSION  
ON  
S. 1217  
TO REGULATE ACTIVITIES INVOLVING RECOMBINANT  
DEOXYRIBONUCLEIC ACID  
AND RELATED BILLS

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APRIL 6, 1977



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WASHINGTON : 1977

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(II)



## CONTENTS

Text of:	Page.
S. 1217-----	10
S. 621-----	28
S. 945-----	36

### CHRONOLOGICAL LIST OF WITNESSES

APRIL 6, 1977

Bumpers, Hon. Dale, a U.S. Senator from the State of Arkansas-----	50
Metzenbaum, Hon. Howard M., a U.S. Senator from the State of Ohio-----	55
Dukakis, Hon. Michael, Governor, Commonwealth of Massachusetts-----	66
Califano, Hon. Joseph A., Jr., Secretary, Department of Health, Education, and Welfare, accompanied by Donald S. Fredrickson, M.D., Director, National Institute of Health; and Ken Levine, Deputy Assistant for Legislation-----	78
Holman, Halsted R., Ph. D., professor of medicine, Stanford Medical Center; Norton Ziner, Ph. D., professor, Rockefeller University; Alexander Rich, Ph. D., professor of biophysics, Massachusetts Institute of Technology; and Hariyn O. Halvorson, Ph. D., president, American Society for Microbiology, a panel-----	119
Hayes, Daniel, former mayor, City of Cambridge, Mass., and chairperson, Cambridge Experimentation Review Board, and David Clem, member, Cambridge City Council-----	167
Stetler, C. Joseph, president, Pharmaceutical Manufacturers Association, accompanied by John G. Adams, PMA vice president, scientific and professional relations; and Bruce J. Brennan, PMA vice president and general counsel-----	176
Warren, Jacqueline M., Environmental Defense Fund, accompanied by Leslie Dach, staff science associate-----	197
Lippe, Pamela, Friends of the Earth, and Jeremy Rifkin, People's Business Commission-----	214

### STATEMENTS

Bumpers, Hon. Dale, a U.S. Senator from the State of Arkansas-----	50
Byrne, Hon. Brenda T., Governor, State of New Jersey, prepared statement-----	71
Califano, Hon. Joseph A., Jr., Secretary, Department of Health, Education and Welfare accompanied by Donald S. Frederickson M.D. Director, National Institute of Health; and Ken Levine, Deputy Assistant for Legislation-----	78
Prepared statement-----	80
Dukakis, Hon. Michael, Governor, Commonwealth of Massachusetts-----	66
Prepared statement-----	75
Frederickson, Donald S., M.D., Director, National Institutes of Health, prepared statement-----	101 ✓
General Electric, prepared statement-----	402
Halvorson, Hariyn O., Ph. D., president, American Society for Microbiology, prepared statement-----	147
Hayes, Daniel, former mayor, City of Cambridge, Mass., and chairperson, Cambridge Experimentation Review Board, and David Clem, member, City Council-----	167

## IV

Holman, Halsted R., Ph. D., professor of medicine, Stanford Medical Center; Norton Ziner, Ph. D., professor, Rockefeller University; Alexander Rich, Ph. D., professor of biophysics, Massachusetts Institute of Technology; and Hariyn O. Halvorson, Ph. D., president, American Society for Microbiology, a panel.....	119
Lippe, Pamela, Friends of the Earth, and Jeremy Rifkin, People's Business Commission.....	214
Prepared statement.....	228
Metzenbaum, Hon. Howard M., a U.S. Senator from the State of Ohio.....	55
Prepared statement.....	60
Rich, Alexander, Ph. D., professor of biophysics, Massachusetts Institute of Technology, additional statement.....	128
Stetler, C. Joseph, president, Pharmaceutical Manufacturers Association, accompanied by John G. Adams, PMA vice president, scientific and professional relations; and Bruce J. Brennan, PMA vice president and general counsel.....	176
Prepared statement.....	184
Warren, Jacqueline M., Environmental Defense Fund, accompanied by Leslie Dach, staff science associate.....	197
Prepared statement.....	203

## ADDITIONAL INFORMATION

## Articles, publications, etc.:

Advocates, The, Friends of the Earth, taken from the WGBH Declaration of Independence, "The Case for Programming Independence".....	240
Comments of the Natural Resources Defense Council, Inc. on the National Institutes of Health guidelines for research involving recombinant DNA molecules and the draft environmental impact statement on recombinant DNA research guidelines, November 1, 1976.....	271
Comments on the draft environmental impact statement for the NIH guidelines for research involving recombinant DNA molecules, submitted to the Director of NIH, October 18, 1976, by Burk K. Zimmerman, Ph. D., staff scientist, Environmental Defense Fund.....	249
Comparison of Cambridge Experimental Review Board and administration proposal.....	178
Excerpts from Science, April 8, 1977, volume 196, No. 4286.....	408
Interim report of the Federal Interagency Committee on Recombinant DNA Research: Suggested elements for legislation, March 15, 1977.....	337
Petition of Environmental Defense Fund, Inc., and Natural Resources Defense Council, Inc., to the Secretary of Health, Education, and Welfare to hold hearings and promulgate regulations under the Public Health Service Act governing recombinant DNA activities.....	381
Responses to propositions and questions in preamble to S. 1217.....	194
S. 1217, introductory remarks of Senator Kennedy, from the Congressional Record, April 1, 1977.....	2
Testimony of Friends of the Earth before the Subcommittee on Health and Environment, Committee on Interstate and Foreign Commerce, House of Representatives, March 16, 1977, by Pamela Lippe.....	241
"Who Should Play God?" by Jeremy Rifkin, director, Peoples Business Commission, Washington, D.C., April 6, 1977.....	301
Communications to:	
Ahmed, Karim A., Dr., Natural Resources Defense Council, Inc., from Robert L. Sinsheimer, chairman, October 28, 1976.....	377
Mathews, Hon. David, Secretary, Department of Health, Education, and Welfare, from Burk K. Zimmerman, Ph. D., staff scientist, Environmental Defense Fund, November 11, 1976.....	376
Solomon, Neil, M.D., secretary of health, States of Maryland, from Robert W. Hicks, Ph. D., biomedical engineer, Washington, D.C., April 2, 1977 (with enclosures).....	310
Zimmerman, Burk, Dr., staff scientist, Environmental Defense Fund, from Alan McGowan, president, November 5, 1976.....	379
Charts:	
Relative distribution of U.S. patents derived from Government and non-Government expenditures, 1970-75, Friends of the Earth, chart.....	239
Research and development expenditures, Friends of the Earth, chart.....	238



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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20014

STATEMENT BY  
DONALD S. FREDRICKSON, M.D.  
DIRECTOR, NATIONAL INSTITUTES OF HEALTH  
ON RECOMBINANT DNA TECHNOLOGY  
BEFORE THE  
SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH  
OF THE  
SENATE COMMITTEE ON HUMAN RESOURCES  
APRIL 6, 1977

# I. INTRODUCTION

Good day, Mr. Chairman and other Committee members. It is a pleasure to have the opportunity to discuss with you Federal policies concerning recombinant DNA techniques. The focus of my remarks will be the activities of two organizations--the National Institutes of Health and the Federal Interagency Committee on Recombinant DNA Research.

As you know, recent scientific developments in genetics, particularly in the last four years, have culminated in the development of a powerful new tool for research--the ability to join together genetic materials in cell-free systems to form recombinant DNA molecules. I would like to emphasize the point that recombinant DNA is a tool for accomplishing the types of research that scientists have been pursuing for decades.

"DNA"--which is the shorthand way of saying "deoxyribonucleic acid"--is the material that determines hereditary characteristics of all known cells. These new techniques allow us to join together DNA segments from different sources or to rejoin the DNA from one source in a different order. This new and powerful tool of science has generated great hope and excitement and, concomitantly, many expressions of concern.

Research using recombinant DNA techniques offers great promise for better understanding and improved treatment of human diseases. Medical advances through use of this technology include the opportunity to explore complicated diseases and the functioning of cells, to better understand a variety of hereditary defects, and possibly (in the future)



## 2

to create microorganisms useful in producing medically important substances for the treatment and control of disease. Aside from potential medical benefits, a variety of other applications in science and technology are envisioned. An example is the large-scale production of enzymes for industrial use; and potential benefits in agriculture include the enhancement of nitrogen fixation in certain plants and the biological control of pests, permitting increased food production.

There may be risks in this new research area as well as anticipated benefits. A potential hazard, for example, is that the foreign DNA microorganism may alter the host in unpredictable ways. Should the altered microorganism escape from containment, it might infect human beings, animals, or plants, causing disease or modifying the environment.

Until the potential risks are better delineated and evaluated in light of developing scientific knowledge, the public should expect such research to be conducted under strict conditions ensuring safety. This was the fundamental principle that guided the National Institutes of Health and the Federal Interagency Committee in their deliberations. That is, the desire to allow this significant research to continue while protecting humans and the environment from the effects of potential hazards whose nature and the occurrence of which is as yet uncertain. I would like to review with the Committee the activities of the NIH in developing guidelines to govern this research, and then devote the rest of my testimony to the work of the Interagency Committee.

## II. DEVELOPMENT OF THE NIH GUIDELINES

The first step in the development of the Guidelines was taken by the scientific community. Scientists engaged in research using recombinant DNA technology first expressed concern about the potential biohazards at the Gordon Research Conference on Nucleic Acids in July 1973. At their request, the National Academy of Sciences created a committee that called for a moratorium on certain types of experiments and for an international conference to consider this problem further. The committee also called on the NIH to establish an advisory committee to study containment procedures and draft guidelines for the conduct of this research. At the International Conference on Recombinant DNA Molecules held at Asilomar, California, in February 1975, temporary guidelines were issued, including a continued moratorium on some experiments but allowing others to proceed with appropriate biological and physical safeguards, pending issuance of NIH guidelines.

The NIH Recombinant DNA Molecule Program Advisory Committee was established in October 1974 to advise the Director of NIH. In December 1975, the Committee, after several open meetings, recommended proposed guidelines for my review and decision.

To assist me in the review of the proposed guidelines, a special meeting of the NIH Advisory Committee was convened in February 1976. Members of the Committee represented not only science but such other disciplines as law, ethics, and consumer affairs. Comments received from committee members and a number of public witnesses represented a

wide range of views. Follow-up written comments were also solicited. In April, the NIH Recombinant Advisory Committee considered these comments from the February meeting, and a number of changes to the guidelines were made. Concurrently, meetings for information exchange were held with representatives from other Federal agencies and private industry as well as with Congressional staffs. Finally, on June 23, 1976, with the approval of the Secretary of HEW and the Assistant Secretary of Health, the NIH issued guidelines to govern the research it supports involving recombinant DNA molecules. The NIH Guidelines established strict conditions for the conduct of this research, prohibiting certain types of experiments and requiring special safety conditions for other types. The provisions were designed to afford protection—with a wide margin of safety—to workers and the environment. Two weeks later, on July 7, 1976, the NIH Guidelines—together with a document indicating the basis of my decisions on principal issues—were published in the Federal Register for public comment.

Over 40,000 copies of the Guidelines have been widely distributed to foreign embassies, medical and scientific journals, NIH grantees and contractors, and major professional research societies.

### III. NIH ACTIVITIES FOLLOWING RELEASE OF THE GUIDELINES

Subsequent to the release of the Guidelines, NIH initiated several actions.

#### A. Office of Recombinant DNA Activities

To facilitate implementation of the Guidelines, the NIH, in June 1976, established the Office of Recombinant DNA Activities: to administer and coordinate intramural and extramural activities at the NIH; to review the institutional biohazards committees; and to monitor reports and information concerning accidents, containment, and safety research innovation.

#### B. Published Proceedings

In August 1976, the NIH published a volume containing the transcript of the February NIH public hearing on the proposed guidelines, voluminous related correspondence, and the results of relevant meetings held prior to the release of the Guidelines in June. A second volume is planned for publication in late Spring documenting the correspondence that the NIH received on the Guidelines, the Environmental Impact Statement, and the Departmental patent policy.

#### C. Environmental Impact Statement

The NIH, in accordance with the National Environmental Policy Act of 1969, undertook an environmental impact assessment to review environmental effects, if any, of research that may be conducted under the Guidelines. The NIH Guidelines were released prior to the completion



of the assessment because they provide greater protection for the public and the environment than the Asilomar Guidelines or no guidelines.

A Draft Environmental Impact Statement was filed and published in the Federal Register on September 9, 1976, to afford additional public review and comment. The draft statement has been analyzed and comments received are addressed in the final Environmental Impact Statement to be published soon.

#### D. Department Patent Policy

In June, shortly before the release of the Guidelines, Stanford University and the University of California asked NIH to review DHEW policies relating to the patenting of inventions perfected through the use of recombinant DNA techniques and financed by NIH. Under current DHEW patent regulations, invention rights to discoveries developed under the Department's research support are normally allocated in either of two ways:

- The Department may enter into an Institutional Patent Agreement (IPA) with a university or other nonprofit institution that has adequate mechanisms for administering patents on inventions. The IPA provides the institution the first option to own all inventions made in performance of Department grants or contracts, subject to a number of conditions deemed necessary to protect the public interest.
- For those institutions that have not entered into a patent agreement with the Department, determination of ownership is deferred until an invention has been made, at which time an institution may petition the Department for ownership of the invention.

The NIH solicited opinions from a number of different groups in the scientific community and the public and private sectors concerning departmental patent policies, with respect to recombinant DNA research inventions. An analysis of the issues raised by the commentators is currently under review.

#### IV. THE INTERAGENCY COMMITTEE ON RECOMBINANT DNA RESEARCH

I would now like to devote the remainder of my testimony to the activities of the Interagency Committee on Recombinant DNA Research. This Committee was created, with the approval of President Ford, to address extension of the NIH Guidelines beyond the NIH, to the public and private sectors.

The specific mandate of the Interagency Committee is as follows: to review the nature and scope of all recombinant DNA research conducted in the United States, to determine the applicability of NIH standards to regulate this research nationally, to recommend mechanisms to ensure that the standards are being complied with, and to facilitate exchange of information throughout the Federal sector. The Committee is advisory to the Secretary of Health, Education, and Welfare. It includes representatives of Federal Departments and Agencies that support and conduct recombinant DNA research (or may do so in the future), and representatives of Federal Departments and Agencies that have present or potential regulatory authority in this area. At the Secretary's request, I serve ~~as~~ Chairman of the Committee.

Two meetings of the Committee were held in November 1976. The first of these, on November 4, was devoted to a review of the development of the NIH Guidelines. The Committee also reviewed activities in other countries on the development of guidelines for this research. Recombinant DNA research is being conducted in a number of countries, including Canada, the United Kingdom, the Scandinavian countries, most other parts of western Europe, eastern Europe, the Soviet Union, and Japan.

In many countries, appropriate governmental or scientific bodies have reviewed the research and have agreed that it should proceed. Several of the countries have acted to establish guidelines to govern the conduct of this research, including the United Kingdom and Canada. In the United Kingdom, a parliamentary committee addressed the issue and indicated that work in this area should continue under appropriate safety conditions. Scientific advisory committees of international organizations, such as the World Health Organization, the International Council of Scientific Unions, and the European Molecular Biology Organization, have made similar recommendations.

The European Science Foundation, representing member nations from Western Europe and Scandinavia, has recommended to its members that they follow the guidelines of the United Kingdom. These guidelines are, in intent and substance, very similar to those of the National Institutes of Health. The NIH is currently working very closely with the United Kingdom and the European Science Foundation to ensure a commonality of

standards in carrying out this research. Thus far, there has been very close cooperation and coordination among the various international and national scientific bodies, with a view to reaching a consensus on safety practices, programs, and procedures.

At the meeting of the Committee held on November 23, 1976, the Federal research agencies discussed their activities and possible roles in the implementation of the NIH Guidelines. All research agencies endorsed the Guidelines to govern recombinant DNA research. At present, the NIH, the National Science Foundation, the Veterans Administration, and the U.S. Department of Agriculture are supporting or conducting such research. The Department of Defense, National Aeronautics and Space Administration, and the Energy Research and Development Administration do not at present conduct such research, but all have endorsed the NIH Guidelines to govern future research should it be undertaken.

#### A. Subcommittee Review of Existing Legislation

Also at the November 23 meeting, the Federal regulatory agencies reported on their regulatory functions. Following that review, a special Subcommittee was formed to analyze the relevant statutory authorities for the possible regulation of research involving recombinant DNA technology. All regulatory agencies were represented on the Subcommittee, assisted by attorneys from their offices of general counsel.

The Subcommittee was charged to determine whether existing legislative authority would permit the regulation of all recombinant DNA research in



the United States (whether or not federally funded) and would include at least the following regulatory requirements:

- (1) Review of such research by an institutional biohazards committee before it is undertaken.
- (2) Compliance with physical and biological containment standards and prohibitions in the NIH Guidelines.
- (3) Registration of such research with a national registry at the time this research is undertaken (subject to appropriate safeguards to protect proprietary interests).
- (4) Enforcement of the above requirements through monitoring, inspection, and sanctions.

It was the conclusion of the Subcommittee that present law could permit imposition of some of the above requirements on much laboratory research involving recombinant DNA techniques, but that no single legal authority or combination of authorities currently existed that would clearly reach all research and other uses of recombinant DNA techniques and meet all stated requirements. Although there is existing authority that might be interpreted broadly to cover most of the research at issue, it was generally agreed that regulatory actions taken on the basis of any such interpretation would probably be subject to legal challenge. The Subcommittee, in reaching this conclusion, reviewed the following laws that were deemed to warrant detailed consideration:

- (a) The Occupational Safety and Health Act of 1970 (Public Law 91-596)
- (b) The Toxic Substances Control Act (Public Law 94-469)
- (c) The Hazardous Materials Transportation Act (Public Law 93-633)
- (d) Section 361 of the Public Health Service Act (42 U.S.C. 264).

In addition, several other laws were examined. The Clean Air Act, the Federal Water Pollution Control Act, the Resources Conservation and Recovery Act, and the authorities of the FDA and the Department of Agriculture.

The full Committee adopted the report of its Subcommittee and agreed that new legislation was required.

B. Interagency Committee Analysis of Elements for Legislation

In considering the elements for legislation, the Committee reviewed Federal, State, and local activities bearing on the regulation of recombinant DNA research.

Among Congressional proposals reviewed were S. 621, "The DNA Research Act of 1977," introduced by Senator Dale Bumpers, and the companion measure introduced by Representative Richard L. Ottinger in the House (H.R. 3591). The Committee also noted the resolution introduced by Representative Ottinger on January 19, 1977 (H. Res. 131), requesting DHEW to regulate recombinant DNA research under Section 361 of the PHS Act.

Among State and local activities reviewed were recommendations by the New York State Attorney General's Environmental Health Bureau for State regulation, and the Cambridge (Massachusetts) City Council's resolution on recombinant DNA research.

Several committee representatives also reported on meetings with other interested parties whose views had been solicited on legislation to regulate recombinant DNA research. Those who were contacted include agricultural scientists, biomedical scientists, environmentalists, labor unions, and private industry. At my request, the Industrial Research Institute and the Pharmaceutical Manufacturers Association are surveying their member firms to determine the scope of the research efforts in the private sector. The Pharmaceutical Manufacturers Association has endorsed the NIH Guidelines as standards for conduct of this research.

In considering elements of proposed legislation, a number of issues were raised and discussed fully by the Committee. After detailed deliberations at meetings on March 10 and 14, 1977, the Committee agreed on a set of elements for proposed legislation. The elements agreed upon and the various alternatives reviewed by the Committee were presented in an Interim Report transmitted to HEW Secretary Califano on March 15, 1977. Secretary Califano, in releasing the report on March 16, stated that "legislation in this area would represent an unusual regulation of activities affecting basic science but the potential hazards posed by recombinant DNA techniques warrant such a step at this time." He went on to say, "...I believe such a measure is necessary not just to safeguard the public but also to assure the continuation of basic research in this vital scientific area. We are not saying that research should be halted. We are urging that it should proceed under careful safeguards unless and until we have a better understanding of the

114

13

risks and benefits posed by use of recombinant DNA techniques ~~without~~ Government regulation."

Mr. Chairman, I would like to submit for the record the Federal Interagency Committee's "Interim Report on Suggested Elements for Legislation," along with a copy of the Secretary's press release.

With your permission, I would like to review briefly some of the major elements addressed by the Committee. The Committee determined that the Department of Health, Education, and Welfare is the appropriate locus in the Government for the regulation of the use and production of recombinant DNA molecules. In reaching this determination, the Committee took into account existing roles of certain agencies within DHEW—for example, that of the NIH in developing the Guidelines, and of the Center for Disease Control and Bureau of Biologics (FDA) in regulating infectious agents and biological products. The Committee also had before it the petition by the Environmental Defense Fund, requesting DHEW to issue regulations for recombinant DNA research.

The Committee reviewed at great length the nature and scope of regulation. Consideration was given to regulation of all laboratory research where hazardous or potentially hazardous substances were employed. There was general Committee agreement that present legislation should be restricted to recombinant DNA techniques.



However, I have established a committee at the NIH, chaired by Dr. Richard Krause, Director, NIAID, to study and recommend, if necessary, safety standards for other NIH-supported research involving actual or potential biohazards. The preliminary report is expected shortly, and I will keep the Committee informed of the progress on this NIH review.

Regulation of just the research aspects of recombinant DNA techniques presents a problem because of the difficulty in determining the border between research and pilot production. Therefore, the Committee recommends that regulation cover the production or use of recombinant DNA molecules. Such language would include research activity, and makes immaterial possible concerns whether a given activity constitutes research, pilot production, or manufacture. The Committee recommends that the Secretary, in specific instances, in consultation with appropriate regulatory agencies, be allowed to determine the nature of the activity and should defer to a regulatory body that the Secretary determines is better empowered and equipped to deal with it.

There was general agreement by the Committee that registration of projects involving the use or production of recombinant DNA molecules was necessary. The Committee also recommends that facilities be licensed and that the terms of the license include acceptance of responsibility for the particular activities and individuals at the facility. The Committee concluded that licensure of the facility and registration of projects would be more feasible and would more adequately meet the needs

for safety monitoring rather than licensure or registration of individuals engaged in research.

The Committee urges full disclosure to the appropriate regulatory body of all relevant safety and scientific information pertaining to the use or production of recombinant DNA molecules. However, the Committee recognizes the important world-wide commercial potential of recombinant DNA molecules in medicine, agriculture, and other areas of science and technology. It believes that the potential commercial uses of recombinant DNA techniques require that information of a proprietary nature and patent rights be given the appropriate protection from disclosure by the regulatory agency receiving such information as is currently provided by existing law. However, the Secretary may immediately release information if public safety requires it.

Because the potential hazards posed by the use of recombinant DNA techniques extend beyond the local to the national and international levels, the Committee recommends that a single set of national standards must govern and that, accordingly, local law should be preempted to ensure national standards and regulations. The Committee, however, took into account the activities at the State and local levels on regulation of recombinant DNA research. It was agreed that, if a State passes a law imposing requirements identical to those contained in the Federal legislation, then the Secretary may enter into an agreement with the State to utilize its resources to assist the Secretary in carrying out his duties.

Protection of workers was also considered by the Committee.

Training of workers in proper laboratory techniques and long-term medical monitoring are important aspects of worker safety and were endorsed by the group.

A number of other recommendations are made, and I can discuss them further if you have questions. I would like to emphasize that the work of the Interagency Committee has been done in a most cooperative and helpful way.

DHEW will continue to cooperate and coordinate with relevant Federal Departments and Agencies in this important matter.

#### IV. CONCLUSION

In conclusion, this much is clear: the international and national scientific community is in substantial agreement that, until the potential hazards of recombinant DNA techniques are better understood, a common set of standards must everywhere exist for the use of those techniques. The question being debated now is how this is to be accomplished. The substance of all guidelines is sufficiently similar; how to apply them locally and nationally remains the issue.

In the United States, this question has attracted far more public attention than in other countries. Indeed, a number of local jurisdictions or States are engaged in action or debate.

Finally, I want to note that biomedical research is entering a new era in its relationship to society. It is passing from an extended period of relative privacy and autonomy to an engagement with new ethical, legal, and social imperatives under concerned public scrutiny. NIH has responded to these concerns by requiring the formation of review boards to oversee human experimentation, animal care, and now DNA recombinant experiments. Similar bodies may soon have to oversee other hazardous laboratory work. These responsibilities are inescapable adjustments to the rising demand for public governance of science, though this need not--and, indeed, should not--go beyond what is clearly required for public safety lest we inadvertently impede successful research and hamper creativity. The progress of science will continue to depend on the initiative and insights--call it inspiration, if you like--of individual scientists.



RECUMBENT DNA: OUR LATENT DOWRIES OF NATIVE ABILITY 1/by Donald S. Fredrickson, M.D. 2/

Before arriving here this evening I gave some considerable thought--and received much advice--as to what salutation would be most appropriate tonight . . . .

My first thought was to begin with a cheery "Good Evening, Fellow Students . . ." After all, you are genuine students and won't resent my satisfaction in pretending. Some of you may know the nice story Goodman Ace contrived for mixed company: [Joke] . . .

But you're not just students; you are students of science. And this binds us together in a special way. For you are learning to savor that special aesthetic experience which is discovery. And you are learning about the long periods of careful, disciplined work that often intervene between the brief moments of discovery.

The hard work is not limited to performing long experiments, but is as much the time taken to prepare your mind. For the most successful scientist is the one whose mind is ready to "make the connection" between two facts or events that to the untrained mind bear no relationship.

If you've begun to get a feeling that nothing else could be as exciting as dedicating yourself--finding your thing--in this kind of disciplined search, then you and I have a special kinship that nothing can destroy.

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1/ For presentation at the Fifth Annual Xavier University-MBS Biomedical Symposium, New Orleans, Louisiana, April 12, 1977

2/ Director, National Institutes of Health, Bethesda, Maryland

Because we've got the same goal in life--to seek the truth.

This important goal we share--you and I--is the reason why one who helped me think of my remarks to you this evening suggested that I start then by greeting all of you as "My fellow members of minorities." The distinguishing feature of the American social structure is that each of us is a member of--or, at least, has deep-set roots in--a racial, ethnic or cultural group that, whatever its size, is but a small part of the conglomerate of peoples who are collectively labeled "Americans." All of us are hybrids with roots in more than one racial or ethnic group but we retain some characteristics of physique, demeanor, and outlook that betray our origins and, in subtle--and sometimes brutal--ways, affect our lives. We are proud, individually and collectively, of our heritages and the infinite range of skills, and the intellectual proclivities, and the cultural traditions they have contributed to the American psyche. But we have, as a nation, failed to make full use or adequately to exploit for the common good the latent Dowries of Native Ability of our Black, our Spanish-surnamed, and our Native American compatriots. The country needs the environmental impact of this recumbent DNA.

[Harold Amos story]

I would compare the peoples of most other countries to loaves of bread: in each case, the dominant ingredient is flour; from which grain, and how the flour was milled, determines its character--whether it is light or heavy; soft or crusty; white, various shades of brown, or almost black, like pumpernickel. But each loaf, whatever its origin, is homogeneous;

its separate pieces are all alike. We Americans, however, are like a rich fruitcake with ingredients from many sources which, though mixed, chopped and blended, retain their individual identities and flavors even while contributing to the texture and flavor of the whole.

This unity in diversity characterizes our way of life and is, I believe, our greatest strength. It distinguishes our government and our politics from those of most other countries. Our two political parties, unlike their counterparts abroad, are not rigidly structured on class, religious, economic or ideological lines but have been described as shifting amalgams of concurring minorities. Our political and social history is replete with examples of the repression of and the struggle

for power--and for a place in the sun--by German-Americans, Irish-Americans, Italo-Americans, Polish-Americans, and more recently--Afro-Americans, Spanish-Americans, and Native Americans. Each group that makes its way into the seats of power will, of course, resist the onslaught of the next--a normal human reaction--but each success weakens the barriers and each group's victory ultimately helps some other group to win.

What is relatively new in American politics is the willingness on the part of the minorities in power to help those still striving for it. (I should note, parenthetically, that it is the practice of those who have arrived to use the word 'minorities' only to describe those who have not. In American politics, it is not a majority that wins, but the collective minority winners who are the majority.) You will say--and you are right in saying--that actual performance in this regard still falls far short of the piously stated intent but you can hardly deny that the prospects are very much better now than there is, at least, a commitment to an intent than when there was not.

When Mr. Califano, the new Secretary of HEW, announced my reappointment, as the Director of NIH, to the NIH staff, he also spoke of the need to keep NIH free of political influences. He said:

"I will do my best to insulate these Institutes and this great institution from partisan politics....there will be no partisan politics involved in any of the work you do, in any of the appointments that are made to any of the Institutes, or any of the committees advising the Institutes. I bring that message not only from myself but from a President who fully recognizes the importance of providing an apolitical environment in which you can work."



But, he added,

"You should know that depoliticizing NIH does not mean....that scientists can be removed from human concerns.....

It does not mean that you are free from the pressure and encouragement that I would impose throughout this Department to deal with the problems of minorities--Blacks, Chicano, Indian, other minorities, women, and the disadvantaged--and to provide them an equal chance with everyone else. It is imperative....that places like NIH use the leadership that they so richly have--and use the leverage that they have in the private sector with the universities who are training people--to enlarge that pool of Blacks and women and Chicanos and minorities--and of handicapped people--that are available for the top jobs in this country. ....

I want to do nothing to inhibit the excellence of the research universities but I will not stand for what I consider to be a myth that excellence is inconsistent with opening those universities and their postgraduate schools to the Blacks and women and other minorities in this country that for so long have had so much difficulty getting into those doors.

I say in a nonpolitical way that we've lost eight years on this problem. I'm not naive enough to think that we can make up those years in four, but we're going to try to make up for some of them. There is no way to do it unless it is done at the top....

It's too easy for the great universities of this country to say, "Well, sure, we'd love to have a professor or researcher or an investigator in that area who's a woman or who's Black, but there just aren't any." If that's true--and I doubt it--to the extent there aren't enough, it's because those same universities haven't opened those doors wide enough. If you open the doors, they'll open the doors. And when you tell them how important you think that is, they'll recognize how important it is. If you can do it here, it can be done anywhere in the world, because you're the best--this is the best place of its kind in the world.

I believe that, President Carter believes that, and you've got to provide leadership in that difficult area."

That is what Mr. Califano said and he got a standing ovation from the NIH audience that filled the auditorium in our Clinical Center.

NIH, of course, already has several programs aimed at achieving the goals that the Secretary described. We are here for the fourth annual symposium on one of them. Some of you will recall that last year Dr. Ronald Lamont-Havers, the Deputy Director of NIH spoke at your meeting and that two years ago NIH was represented by Dr. Thomas Malone, the Associate Director for Extramural Research and Training. Dr. Lamont-Havers has retired from NIH, to become the Deputy for Research Policy and Administration at the Massachusetts General Hospital, and I have just appointed Dr. Malone to succeed him as Deputy Director. This has been the normal progression: Dr. Lamont-Havers and his predecessor, Dr. John Sherman, had both served as Associate Director for Extramural Research and Training before they

became Deputy Director. I mention this because Dr. Malone is Black and it is unfortunately fashionable these days to assume, when a Black is appointed to a senior position, that this is a gesture toward Upward Mobility. NIH can't afford to indulge in such cynical cosmetics. Mr. Califano, in a part of his speech which I have not quoted, said that the only quid pro quo he wanted for keeping politics out of NIH was excellence: excellent appointments to advisory committees, excellent Directors and staffs, and excellent work. By appointing Tom Malone, we gave Mr. Califano what he wanted.

It is still a common misconception--at least among non-Blacks--that Blacks are only now beginning to attain positions of responsibility and influence in the medical sciences and in biomedical research. We at NIH know how false that impression is. Last September, as part of the NIH celebration of the Bicentennial, we unveiled a portrait of Dr. Charles Drew-- a Black physician who was born in Washington in 1904. After attending public schools in Washington, he received an A.B. degree from Amherst College and his medical education at McGill University. He did his internship and residency in medicine in Montreal and his residencies in surgery at Freedman's Hospital in Washington and Presbyterian Hospital in New York, meanwhile working on a Doctorate in Medical Science which he received from Columbia University in 1940. During World War II he was so successful in improving the procedures for blood and plasma collecting that he is rightly honored as the Father of the Blood Bank and is credited with having made a major contribution to the saving of countless American and allied lives. It is ironic that, at the time, his own blood was not acceptable in American blood banks because he was Black. In 1944, he received the Spingarn Medal of the NAACP and was widely honored with

other awards and citations. It is tragic that his brilliant career was cut short by his untimely death, in 1950, at the age of 46. But his name lives on in the annals of medicine and patients all over the world continue to benefit from his pioneering work.

No one knows how many public benefactions have been lost because so few Blacks--and members of other minorities--have had the educational and professional opportunities that Dr. Drew enjoyed. It is not just a matter of fairness, decency and consideration--important though that is--but the waste of intellectual capital and human resources with which we must be concerned.

For the past 5 years, NIH has, in fact, made a diligent effort to provide support for and stimulate activities that will help to entice minority students into the biomedical sciences and to prepare them for productive and satisfying careers in medical research. However, the primary mission of NIH is to conduct and support biomedical research of the highest quality and its stewardship of public funds demands that monies appropriated for this purpose be spent on projects selected, through a rigorous review process, for their scientific excellence and relevance to the categorical missions of the various Institutes. This process inevitably favors institutions with established reputations and scientists with the highest credentials for research and it is not designed--nor readily adaptable--to assist institutions and their scientific faculties and students to establish the facilities or attain the expertise that are prerequisites for successfully competing for NIH research grants or contracts. With the concurrence of the Congress it was therefore decided to establish special programs whose purpose is the creation of excellence and under which awards can be made on the basis of a potential for excellence rather than its prior existence. For the



general oversight and coordination of these programs, the Associate Director for Extramural Research and Training has on his staff a Special Programs Officer who, as you know, is Dr. Griffo.

The two major operational programs are the Minorities Biomedical Support--or MBS--Program and the Minorities Access to Research Careers--or MARC--Program.

The MBS Program--of which you all are a part--is administered by the Division of Research Resources with Dr. Gonzales as MBS Program Director. It has, as you know, achieved remarkable results in the short time in which it has been in existence. This year it will make awards to 80 minority institutions and involve approximately 1,400 students, 500 faculty members and 100 other staff. The participating institutions are now able also to attract other funds for research--some have qualified for the Biomedical Research Support grants which NIH awards, on the basis of a formula, to institutions heavily involved in biomedical research; investigators supported through MBS have published many useful papers and are beginning to compete successfully for regular NIH research grants--several have qualified for NIH Research Career Development Awards. Dr. Gonzales has in his files a number of letters from students recounting their happy experiences with the MBS program--one, from a student at California State University, Los Angeles, is particularly thoughtful and appreciative though it ends on a note of frustration: the letter concludes

"I find myself in the position of wishing certain words and phrases had never attained the level of cliches, so that I might now use them unhesitatingly to express how grateful I am for the opportunities which the MBS program gave me."

But the credit for the success of the MBS program--or of the other minority-assistance programs I shall mention--does not belong to NIH but to you who have taken advantage of the opportunities it affords. The success of any developmental or training effort depends, in the final analysis, on the willingness, the diligence, and the intelligence of those it is intended to help. NIH can only give you the tools; it is you who are doing the job.

The Minority Access to Research Careers program, which is administered by the National Institute of General Medical Sciences in the manner of one of its regular training programs, is designed to raise the professional competence of biomedical science faculty in minority institutions. It is a two-way street consisting of a Faculty Fellowship Program--that enables faculty members of institutions with a predominantly minority enrollment to attend major universities or professional schools, either to pursue postdoctoral research or to complete the requirements for a Ph.D. degree in the biomedical sciences--and a companion Visiting Scientist Program that enables minority institutions to bring prominent science-scholars at major universities to their campus for all or part of an academic year. There are now some 40 Faculty Fellows at 30 graduate institutions but, thus far, only three awards have been made under the Visiting Scientist Program which, in general, involves more complicated arrangements and was only recently exempted, by special legislation, from the pay-back requirements imposed on the training programs.

A third component of the MARC program has just been announced. This is the Honors Undergraduate Research Training Program which

is designed to provide better preparation of outstanding students at minority institutions for subsequent graduate studies at major universities. This honors program will, initially, be limited to a very small number of really superior students who will be given an opportunity to participate in courses and research training at outstanding institutions that can provide experience not available at their home institutions. Some obstacles still have to be overcome. I have requested a change in the Federal Regulations that now prohibit the training of pre-baccalaureate students under the MARC program and I am seeking an advance waiver of the pay-back provision of the National Research Training Act for these pre-baccalaureate students.

Programs for developing minority capability in biomedical research fall readily within the missions of the Division of Research Resources--which, as its name indicates, seeks to enhance our national research capability--and the National Institute of General Medical Sciences--which, among other things, supports research and research training in the basic sciences that underlie medicine. They do not fit so readily into the missions of the other Institutes that are focussed on disease-oriented research. These Institutes do, however, support--through the MBS and the MARC programs--a limited number of research projects relevant to their interests. The growth of this cooperative approach--which was discussed here, in some depth, yesterday--will depend on the extent to which research activity in minority institutions is appropriate for disease-oriented projects and, of course, on the number and quality of the proposals

for such projects submitted by these institutions. You should bear in mind that support for disease-oriented research is available and that, indeed, one of the purposes of the minority programs is to enable your institutions to compete for such disease-oriented grants.

As special needs to develop research expertise in particular areas arise, there will also be special programs to involve minority institutions. An example of this approach is the Minority Hypertension Research Development Summer Program which was announced by the National Heart, Lung and Blood Institute last July and will be in operation this summer. This program offers training for faculty members and graduate students of minority institutions at well-established Hypertension Training Centers. At the conclusion of their summer training, the participants will return to their home institution which will have undertaken to provide them with resources for hypertension research. The future of programs of this type will also depend on the need or opportunities that develop in the various Institutes and on the willingness and ability of the minority schools to take advantage of them.

Members of the Heart Institute's staff are here--in the hospitality suite--to discuss the Hypertension and other Institute programs with those of you who are interested.

In order to assist minority and other disadvantaged institutions to take the fullest possible advantage of the various forms of assistance and support available from NIH and the other health agencies in the Department of Health, Education, and Welfare, we are planning to launch an extramural residence program for minorities and women. Under this program, a small



number of staff members--who need not be scientists but who should, preferably, have authority at their institutions--would spend the better part of a year at NIH to acquire a comprehensive knowledge of the available programs, their requirements, and their management so that, on returning to their institutions, they will be able to advise on the development of innovative activities that will result in more effective competition for Federal grants and contracts. Their training, while at NIH, would be similar to that provided under our Grants Associate Program which has been very successful in recruiting and training scientist-administrators to fill management positions at NIH. Initially, we shall probably be able to accommodate only half a dozen extramural residents at any one time but, if the program is successful, its ultimate aim would be to have at least one of its graduates in each minority institution. In short, it is our intent not merely to make research and research training support available to you but to help you to take full advantage of what is available by knowing what to apply for, how to apply most effectively, and how to maximize your chances of successfully competing for an award of a grant or contract.

I am proud of these programs and I hope that you are pleased by the progress they are already making. But I shall be better pleased with them--and you will have reason to be proud--when they cease to exist because they are no longer needed. I am sure we both look forward

... to the day when the potential excellence inherent in the institutions, the faculties and the students that you represent is fully realized;

... to the day when Mr. Califano's charge to NIH can be burned,  
like a paid-up mortgage, because it will have been discharged;  
... to the day when the recumbent DNA, of which I spoke, will  
have been recombined into the genetic make-up of our nation  
and all the Dowries of Native Ability have simply been melded  
into the family fortune.

This will not be accomplished easily or quickly but it will be  
accomplished if we proceed steadily and vigorously along the road that  
we are now traveling together. I hope these useful and inspiring symposia--  
of which this is the impressive fourth--will continue and flourish. But  
not for too long. I know you, too, look forward to the day when the  
Director of NIH will be invited to speak at the last MBS Symposium. Who  
knows, perhaps that Director will be a Spanish-speaking Black--from Hawaii.  
I shall envy her.

## SUGGESTED TEXT FOR DR. FREDRICKSON'S WELCOMING COMMENTS

APRIL 18, 9:10 A.M., WILSON HALL

I welcome you to the National Institutes of Health and to the conference on "Environmental Health and Safety Requirements for Sponsored Research in Higher Education". It is gratifying to see so many universities, institutions, and research organizations represented.

The conference, - the first of its kind -, is most appropriately co-sponsored by the American College Health Association. We felt the need for such a conference very strongly. Let me briefly give you the reasons for this statement:

The mission of the National Institutes of Health is to improve the health of the American people through the conduct, encouragement, and support of health research and development and related activities. In pursuit of this goal, the NIH supports about 37 percent of U.S. medical research and development, and provides about 63 percent of all Federal funds for health research. This significant contribution ~~to the nation's attack on diseases which jeopardize the health and reduce the quality of life for millions of people each year,~~ is accomplished principally through grant and contract awards to academic and other health research institutions, to conduct research and development, develop research specialists, and improve the nation's biomedical communications system.

With the continuing discovery of new knowledge, new health problems have been identified, and others yet unsolved require a renewed effort. The nature of these problems and the demand they place upon the further advance

## 2 - Suggested Test for Dr. Fredrickson's Welcoming Comments

of knowledge and technical capability, to the extent that scientific opportunities exist, are major forces shaping the programs of NIH. About 85 percent of the NIH budget each year supports projects and activities in primarily non-Federal organizations and institutions, conducted under grant or contract awards. Biomedical research at NIH and where it is funded by NIH is increasingly faced with problems related to concerns for environmental health and safety. These problems are many fold and of a wide range. Most are related to public and community concerns for adverse effects on the environment and the physical safety of the employees and visitors.

Concerns, once they become strong enough and generally accepted, are usually expressed in legislation. Consequently, we have seen in the past decade the emergence of a number of laws and Acts, all of which can be construed as being restrictive in one way or the other.

One outstanding example is the National Environmental Policy Act, or NEPA for short. The Act requires each federal agency to consider the environmental effects of proposed actions. This includes NIH funded research.

The Act, as written and passed in 1969, was open to the development of considerable rule making. For DHEW, regulations were issued in 1974, creating new responsibilities for its agencies to document environmental safeguards. These responsibilities extend, for NIH, to the assurance of available safeguards for the protection of the environment and the health and safety of people.



### 3 - Suggested Test for Dr. Fredrickson's Welcoming Comments

Guidelines had to, and will have to, be developed for those subjects of health and safety that are inherent in the broad scope of our intra- and extramural activities. Some, such as the NIH Guidelines for Recombinant DNA Molecule Research, are very specific and explicit. The requirement of an institutional Biohazards Committee is an important stipulation of the guidelines.

Obviously, the college, university and institutional environmental health and safety programs have a key role to play in formulating safeguards, providing guidelines and assuring adherence.

It is the objective of this conference to acquaint you with health and safety guidelines to be followed in the conduct of federally-sponsored biomedical research. The institutional process of development and administration of environmental health and safety policy will be discussed. You are invited to participate in the discussion and to take advantage of any assistance we may be able to offer. It is my distinct pleasure to have you with us here at NIH.

## KENNEDY INSTITUTE--April 26, 1977

In welcoming Dr. H. Tristram Engelhardt, Jr., as the appointee to the first endowed Chair in the Philosophy of Medicine in America--The Rosemary Kennedy Professorship at Georgetown University--Dr. Donald S. Fredrickson, Director of the National Institutes of Health, said:

"It has been said [by Alex Comfort in a BBC talk in 1951] that medicine is the only branch of science which has a unified ethic, and has had it for more than 6,000 years--that the idea of the human responsibility of the physician has been present since medicine was indistinguishable from magic. The principles of conduct to which all graduating medical students are required to subscribe were laid down four centuries before the birth of Christ by Hippocrates.

Because medical ethics are an accepted and integral part of the teachings on which modern medicine is based, one may wonder why we need a Center for Bioethics or why a new chair for the Philosophy of Medicine should be established within it. This question has been thoughtfully explored and cogently answered in the writings of the distinguished scholar who has been chosen as the first incumbent of that chair, Dr. H. Tristram Engelhardt, Jr. It is inappropriate for me to attempt to suggest how he should go about his task. But it is not out of place for me to tell you how grateful I am to the Kennedy Institute for having created this new academic post and brought Dr. Engelhardt here to fill it.

Much of my time during my first 2 years as Director of the National Institutes of Health has been devoted to wrestling with policy questions and administrative problems arising from the rapidly changing relationships between research in the biomedical sciences and the societal setting in which it is conducted. The progress of biomedical research and the development of technology during the past twenty years has been extraordinary. I believe its future promise is even brighter. But as the power of science and technology to affect our lives increases, so also increases the requirement of a stronger ethical framework within which to use those powers.

This phenomenon is not confined to the biomedical sciences. Dramatic developments in genetics, for example, have had their counterpart in nuclear physics and in space technology. These have also created biological, social, and economic concerns--to which must be added the growing apprehensions created by our burgeoning industrial technologies and their effects on man and his environment. Science no longer remains the exclusive province of the scientist. The pace has quickened and experience has shown that even the abstruse fundamental research can lead to consequences that affect much of society.

- 3 -

I believe that the time has come for a reconvergence of science with the philosophical base from which it emerged in the 16th and 17th centuries--not for reasons of convenience or sophistry, but out of sheer necessity. We are inevitably moving toward a closer public governance of science--and its advantages are coupled with considerable danger to the processes of inquiry.

The Kennedy Institute is therefore to be commended for taking the initiative to meet a real and immediate need. My enthusiasm for Dr. Engelhardt's appointment is partly selfish; it will be very helpful to all who are engaged in keeping science at the service of man to have so readily at hand a colleague and consultant whose main concern is tending its troublesome and delicate philosophical roots."



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## DINNER ADDRESS

### AESCULAPIAN MERRY-GO-ROUND\*

By DONALD S. FREDRICKSON†

#### *The Medical Omphalos*

This is the ninetieth year of the Association; perhaps even its ninetieth annual dinner. These venerable rites take shape with an innocent-sounding invitation from the President to the after-dinner speaker. "Just give some humorous vignettes," he says—"some insights . . ." (in my case, about Washington). You think, "That's easy; I'll do it." Time passes; you haven't prepared it and now it's too late. Or worse. Something happens to the proposed topic; you're not sure it's funny anymore.

My ordeal began when I went up to Providence to tell about the location of the Medical Omphalos. I got the idea after listening to Frank Press lecture on plate tectonics at the Academy. There were all these continents shifting around, eventually settling down to form today's map. You will recall that after the Peloponnesus cooled off, the Greeks decided that the center of the earth—the Omphalos—was at Delphi. It was the *medical* center-of-the-earth, too, as this photograph of Aesculapius sitting on the Omphalos clearly demonstrates (Fig. 1†).

I got to thinking how the medical center-of-the-earth had been wandering around, shifting to Padua to Leyden to Vienna to Edinburgh, etc. Oh, it was easy to pretend in Providence§—how the Medical Omphalos had been relocated at Hopkins, moved up to Boston, and maybe out as far as Minnesota. And how, with Hill-Burton and NIH grants, everybody became so equally sophisticated that the Omphalos finally disappeared. But all the time, I had this uneasy feeling. After Hill-Burton came Heart Disease, Cancer, and Stroke, then Medicare/Medicaid, the Catastrophic Illness Amendment, the Health Planning and Resources Development Bill, the Health Manpower Bill; and—no end in sight—this summer will come the Clinical Laboratories Act, the Recombinant DNA Bill, the Cost-Containment Measure, etc.

You've guessed it. The Medical Omphalos is back in business. And this time it's come to Washington, D.C. Maybe for good. Well, for keeps, anyway.

\*Delivered before the Association of American Physicians, Sheraton Park Hotel, Washington, D.C., May 2, 1977.

†Director, National Institutes of Health, Bethesda, Maryland.

‡From Harold Speert's *Iconographia Gyniatrica*, p. 170, F. A. Davis Co., 1973.

§"The Search for the Omphalos," presented at the 50th annual meeting of The Miriam Hospital, May 3, 1976. *Rhode Island Med. J.* 59:454, October 1976.



FIG. 1

With so much at stake, I don't see how we can waste time on "humorous vignettes." We should get right down to a sober analysis of what this town is all about—how medicine and the medical sciences got aboard this carousel on which all the horses are either lawyers or generals—and whether, for medicine, the music is ever going to stop.

*Practitioners and Politicians: Historical Glimpses*

Physicians have always been exposed to temptations—probably a result of constantly carrying the serpent around on the caduceus. One of the strongest temptations is to dabble in politics.

Five of the original signers of the Declaration of Independence were physicians.\* The most famous was Benjamin Rush, the "Great Bleeder," who is the subject of the only outside statue of a physician to be seen in Washington. Statues of six other physicians are tucked away in the crannies of the Capitol.†

Speaking of the Capitol, we should note that it was William Thornton, physician-turned-architect, who designed the first Capitol and supervised its construction until 1802. The early Capitol had a Bulfinch Dome, designed by the same Charles Bulfinch who gave us the Ether Dome at the Massachusetts General. I should note that, while the filibuster is the preferred general anesthesia in the Capitol today, ether was an early favorite of the Congress. After the dentist William T. Morton gave his much touted demonstration in the Ether Dome, a marble likeness of Crawford Long was placed in Statuary Hall in the Capitol to remind America of his earlier claim to the same discovery.

Crawford Long was a surgeon from Georgia, and no relation to Senator Russell Long from Louisiana. Senator Long is chairman of the Senate Finance Committee, which sets fees for Medicare. He may have a greater influence on future medical practice than Dr. Long of ether fame.

The first President to be medically trained was the ninth, William Henry Harrison. "Old Tippecanoe" caught cold at his inauguration and died within a month. The haste with which his campaign pledge—"and Tyler too"—was redeemed apparently unnerved the American voters. They haven't since entrusted the health of the Nation to a physician, although Warren Gamaliel Harding was the son of one.

The sons of physicians have flourished in other Washington roles. The most famous of these was Oliver Wendell Holmes. Holmes gets us back to ether again, for it was his father, also Oliver Wendell and Professor of Anatomy at Harvard, who suggested the term "anesthesia" for the phenomenon induced by Long/Morton.

\*Josiah Bartlett, Matthew Thornton, Oliver Wolcott, Lyman Hall, Benjamin Rush. [Portraits were shown in one of 80 slides, only 7 of which are reproduced with this paper.]

†Ephraim McDowell, John Gorrie, John McLaughlin, Florence Sabin, Marcus Whitman, and Crawford Long.



Another son of a physician, and the greatest political benefactor of medicine and its sciences to date, was Senator Lister Hill, named for the father of antisepsis.

Nearly 400 physicians have been members of Congress at one time or another. At present there are two. Tim Lee Carter of Kentucky, ranking minority member of the House Subcommittee on Health and the Environment, and Rep. Lawrence McDonald, urologist from Georgia and leading Congressional proponent of Laetrile.

The Government has long employed physicians *qua* physicians. The most prominent of these have been the Surgeons General. There have always been military Surgeons General, but long before somebody had to label cigarettes as hazardous, *the* Surgeon General came to mean the commander of the Public Health Service. The fourth of these may have had the most remarkable career. Rupert Blue was not only Surgeon General, but simultaneously for one year was also the president of the American Medical Association. While wearing two hats, Blue promulgated a daring proposal for national health insurance. There is no record that the AMA has considered such a leadership liaison since that time.

But enough for history. Let's pay a visit to the center of things—perhaps even get a glimpse of the elusive Medical Omphalos.

### *Landmarks*

We have time only to pause briefly at some of the sights that make Pierre L'Enfant's city such a pleasant place to visit.

Rounding the somewhat cluttered approach to the Lincoln Memorial, the tourist-photographer comes to the monument to the Father-of-Our-Country. Its egregious symbolism led Washington to become the center of the neo-Freudians, like Karen Horney and Erich Fromm, eager to de-emphasize the master's preoccupation with psychosexual development. Nearby is the beautiful Tidal Basin, in which Ms. Fanne Fox took a celebrated early morning bath in 1975 and washed away the career of the Most-Powerful-Member-of-the-Congress, Mr. Wilbur Mills.

We physicians must attend to four loci of power, located along the Mall:

- *The Capitol.*
- *The new South Portal Building.* At this site are located the offices of Joseph A. Califano, Secretary of Health, Education, and Welfare. In *U.S. News & World Report's* annual poll to determine "Who Runs America," Mr. Califano was judged to be the most powerful person in Health. Mr. Califano's private dining room, a topic of recent press comment, is in this building. Upon hearing that Mr. Califano had hired a cook, House Speaker Thomas (Tip) O'Neill remarked that anyone who pays \$12,000 a year for a cook in this town needs a food-taster!



On these premises, too, are kept the ceremonial flags of the Surgeon General and the roster of his numerous statutory duties. The Surgeon General, however, is not there. He has not been seen for several years.

- *The White House.* A clinic has long existed in the White House for care of the President and his family. Whether a "health desk," for attending to the multiple health programs of interest to the Nation, exists in the White House is uncertain.
- *The Old Executive Office Building.* Next door to the White House is the former State-War-Navy Building. Franklin Roosevelt forced Cordell Hull to yield ever juicier segments of these quarters so that a site might be prepared for the eventual location of the Omb.\* There are several theories on how the Omb got its peculiar name. One attributes it to a misspelling of *ohm*, the unit of resistance. Another suggests that it comes from the Brahman mantra popularized by Allen Ginsberg. This originally contained three sounds, one each for the gods of creation, preservation, and destruction.†

The first sound has been silent since the adoption of Omb by Richard M. Nixon.

To the Omb are sent all proposals for Administration actions. From the Omb are returned the reasons why the actions are too expensive or politically infeasible. In addition, the Omb annually counts the number of Administration employees and supervises preparation of the budget.

These important sources of guidance function together smoothly, linked by moving chains of paper known as "governmental process." To illustrate the workings of governmental process, we have depicted here the major sequential moves made by the budget of the National Institutes of Health (Fig. 2).‡ Unfortunately, neither time nor the resolution of the projector will permit us to analyze the process in detail. We may note, however, that the initial offering undergoes alterations as it traverses the Omb and other stations and is unrecognizable at the end. This was of course anticipated by the Founding Fathers as they created the checks and balances in our government.

### *Government Phyla*

Let us examine a bit more closely the governmental phyla and mores as they affect medicine and health. As every schoolboy knows, there

\*The Office of Management and Budget (OMB) was formed in 1970 from the Bureau of the Budget (BoB), established in 1923.

†See "Om"; *Random House Dictionary of the English Language*, unabridged edition, 1966.

‡NIH is represented in geographic relation to the buildings mentioned above—the Old Executive Office Building, the White House, the South Portal Building of HEW, and the Capitol.

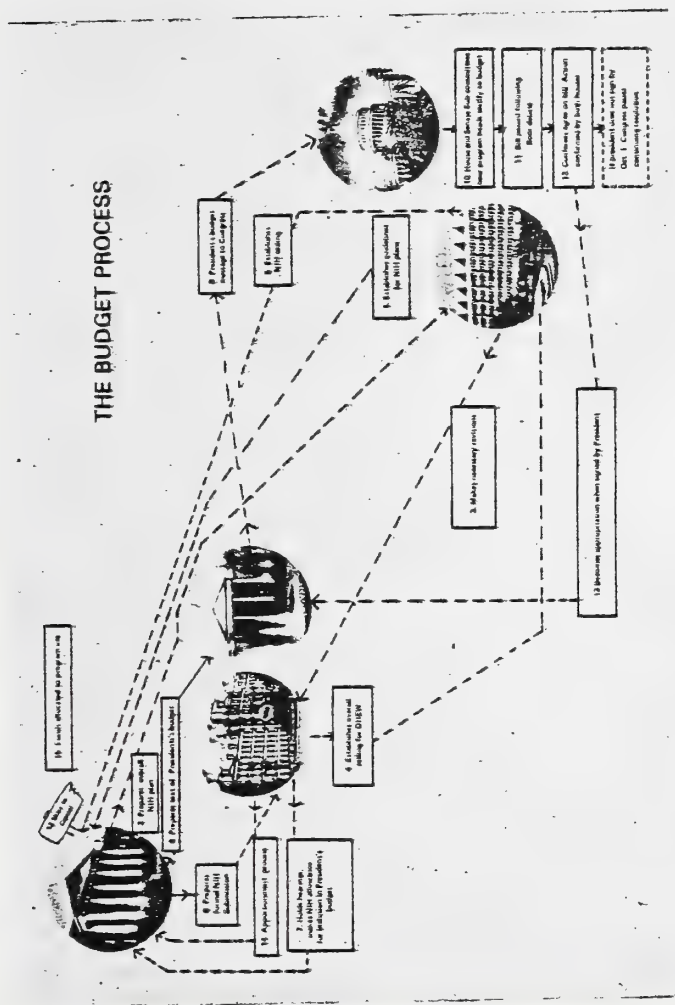


FIG. 2

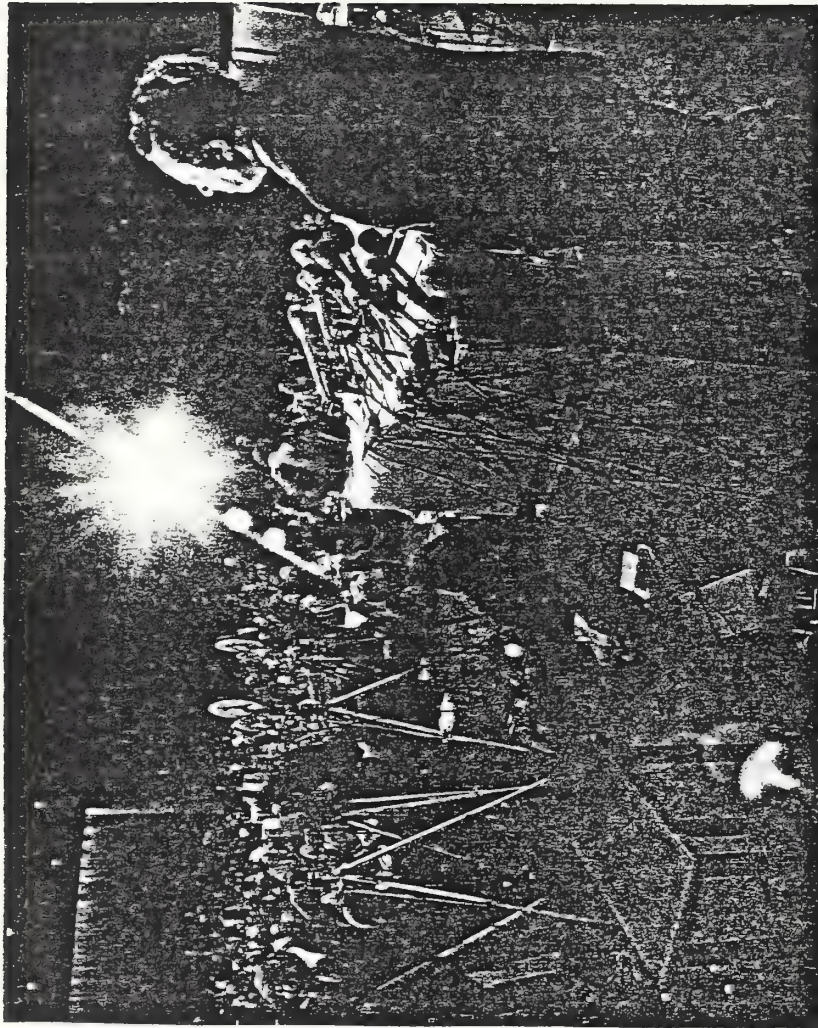


FIG. 3



were three principal Estates in the time of Louis XVI—the nobles, the clergy, and the people. In matters concerning us tonight, the Administration, with its many officials elected and appointed, is the new Second Estate.

I shall have to neglect the new Third Estate for tonight. The role of the Federal Judiciary in regulating medical practice is in its relative infancy, although a robust maturity is predicted.

Since George Washington, Presidents have been purged, bled, and comforted. They have also been incised,\* and advised by physicians like this famous whale electrocardiographer.† The relationship between physician and President has usually been a fairly private affair, however, and no President has ever seen much political advantage in publicly interfering with any of the oldest professions.

The President is regularly affirmed to be the most influential and powerful person in America, and there is no disputing his position in general affairs. In medical affairs, however, the Administration is a late-comer. It was the Congress that first discovered the vulnerable soft spots in the Health Care System. Congress, at least from our point of view, is clearly the First Estate.

We still depend, of course, upon the dendrites and axons of the traditional Fourth Estate to keep us informed of the workings of the first three Estates (Fig. 3). The key proletariat in Washington, however, is the Fifth Estate. The Fifth Estate comprises the bearings upon which the wheels of government turn. Three classes are discernible:

- *The Staffs* are the untenured, indispensable, and now innumerable servitors of the First Estate.
- *The Bureaucracies* represent the tenured, indispensable caste beholden to the Second Estate. They are highly enumerated and begrudgingly apportioned annually in units called "slots" by the miserly Omb.
- *The Lobbies* tend to be deposed members of the other Estates. Their friendliness is assured by generous compensation, correcting any financial sacrifices they have endured in former stations.

### *The Congress*

Although the balance of power is changing, Congress has long been the proposer as well as the disposer in bringing the Federal Government into medicine. Let us study this creature more closely. In forming "a more perfect union," the Founding Fathers first created Congress. In 1787 Congress grudgingly approved a Convention, proposed—they

\*Slide showing President Lyndon B. Johnson pointing to his cholecystectomy scar, from a widely published photograph.

†Paul Dudley White, from *Hunting the Heartbeat of a Whale*, P. D. White, S. W. Matthews, J. B. Roberts; *National Geographic*, CX:49, July 1956.



thought—for the purpose of improving the powers of Congress. As you know, the summer heat in Philadelphia provoked a dreadful wrangle among the delegates, who finally proceeded to apportion the powers of government among *three* branches while dividing the Congress itself into two parts.

The upper house or Senate was to approve treaties and consent to Presidential appointments, unless a Senator from the appointee's home state found the appointee "personally obnoxious."

The more unruly lower house was to initiate all measures appropriating Federal monies and, as we have learned, could draw up bills of impeachment of the President. It seems unlikely that the original intent of either house included the oversight of medical practices.

The Congress came to Washington in 1800 and occupied quarters in the Capitol. There remain the ceremonial and debating chambers of both houses. The real business of Congress, however, is conducted in cavernous structures linked to the Capitol by underground trolleys. To the northeast these run to the Dirksen and Russell Buildings of the Senate. To the south rise the Longworth and Cannon Buildings. These were recently joined by a vast building amalgamating features of the Roman Forum, the Escorial, and the Kremlin. It is named for the late, great Speaker of the House, Sam Rayburn.

To these temples come the supplicants, pleading for funds to promote the general welfare or for relief from the taxes that provide the funds. Where health is concerned, Daniel J. Flood of Pennsylvania and Warren G. Magnuson of Washington are Chairmen, respectively, of the House and Senate Labor/HEW Appropriations Subcommittees. They preside in the places earlier held by John Fogarty and Lister Hill. These predecessors developed legendary prowess in adding funds to Administration budgets so that hospitals might rise and medical schools might meet their indebtedness, and—most notably—they sustained an increasing Federal commitment to support the sciences upon which rational medicine depends.

As the power of the health appropriations committees has increased, to the despair of successive Presidents and the watchful Omb, there have emerged new internal checks. There are now authorizing committees, come to limit the discretion of the appropriators. And lately, congressional budget committees have risen to challenge them both at the new game of "budget quotas."

No Senator is better known than Edward (Ted) Kennedy, Chairman of the Senate Human Resources Subcommittee on Health and Scientific Research. Possessed of a powerful mixture of charisma, ambition, and ability, this survivor of the best known political family of our time has demonstrated a magical power over the blood pressures of countless life scientists, deans, and officials of the AMA, AAMC, or AHA. For the past six years, no member of Government has had a greater single influence on the latter-day structure of the NIH, medical curriculum, residencies, resources, and the deviltries of PSRO's and HSA's. His influence has

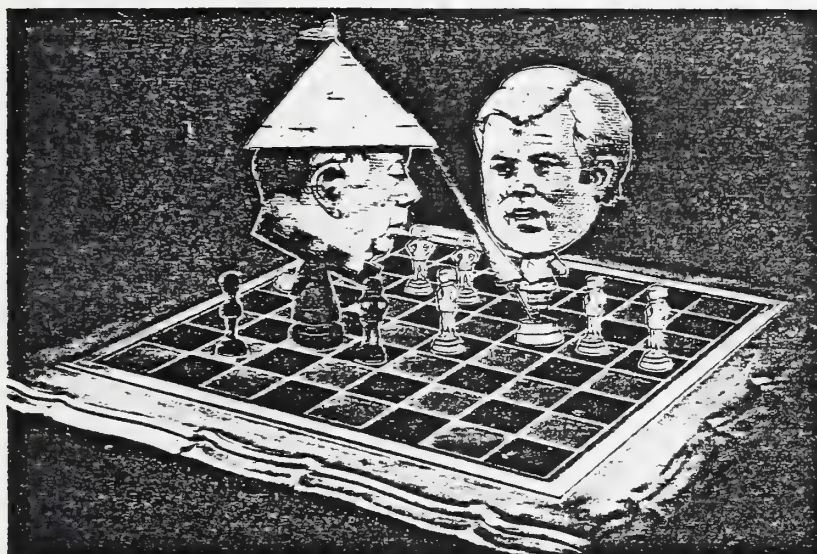


FIG. 4

been crucial in recent legislative commands for regulation of medical devices and forthcoming regulation of laboratories.

But power is balanced here, too (Fig. 4). In the House, Paul G. Rogers and his Subcommittee on Health and the Environment must agree to each incursion upon tradition proposed by the Senate. Operating with a staff pale in numbers to that of his counterpart, Rogers has made some legislative stands of extraordinary importance. Stephen Strickland credits him with successful resistance to a version of the National Cancer Act of 1971 that, in my opinion, would have irreparably damaged biomedical science in this country. There is also that remarkable piece of legislation, the Toxic Substances Control Act of 1976, also known as TOSCA, like the opera. Administered by the powerful Environmental Protection Agency, TOSCA bears a felicitous phrase in her Section 5 which most attribute to Paul Rogers. Section 5 exempts research laboratories from pre-registration of the small amounts of toxic substances they use.

In the Congress, the trades and compromises, the narrow escapes, from which devolve the crucial syntax of statute, are consummated privately. The outcome may or may not bear relationship to input earlier derived from ceremonial public exercises held for the purposes of "creating the record." The hearing is a dramatic form vital to the democratic process. Here is staged the balanced presentation of controversial issues. And here the Congress squeezes on the tender receptors of the Administration to excite responses in its higher centers. A notable feature of

the sharing process is its thoughtful adjustment to the digestive rhythms and high metabolic rate of the media.

It is in the hearings also that one is reminded of the continuity of American culture. Perhaps you've wondered, for example, what ever happened to the Angry Young Persons who stood unshaven at the barricades or trashed the dean's office in the Sixties. Well, some have bought ties and are standing now at the elbows of Congressmen and Senators. As the sit-in becomes a bore, far more effective ways to shake up the musty, elite institutions have emerged in employment on the congressional staff. The hours are awful and the competition is fierce. Their crowded offices overflow to the condemned flats on the fringe of the Capitol. But the compensations are many, particularly in the sense of power and participation in tomorrow's history. Congress and its staff are inseparable and symbiotic. Especially in the case of busy Senators, the apprentice is the caretaker of his master's image—but is allowed to fumble only once.

#### *The Fourth Estate*

The "sunshine laws" have brought powerful new sources of light to play upon the governmental processes (Fig. 5). Here, battery-powered gentlemen of the Fourth Estate are exercising their First Amendment rights on behalf of Channel 5 (WTTG) at a recent meeting on recombinant DNA guidelines. The interruption created by the shock-troops will likely be dissipated on the cutting-room floor or replaced with a clip from "Frankenstein." Thus, the mop-up crews must move in at the finish. Here are three stalwarts of the national science press—Cohn of the *Post*, Schmeck of the *Times*, and Leary of AP—all pumping drops of copy from an exhausted well (Fig. 6).\*

The press, Guardians of the Governed, abound in Washington, in keeping with its ascension to the news capital of the world. In addition to the *Congressional Record*, the city has three daily newspapers—the *Times*, the *Post*, and the *Star*. The first is still printed in New York for sentimental reasons. The second is run by Katharine Graham, winner of a recent poll as the most influential woman in America. This is in recognition of her persistence in bringing down the 37th President of the United States, despite John Mitchell's excruciating image of what would happen to her if she did.

Then there are the numerous stapled sheafs of blue or white or pink sheets which arrive weekly and are passed from desk to desk like *samizdat* literature in Gulag. The fare alternates between complete reproduction of draft memorandums plucked from agency waste baskets and sometimes hilariously inaccurate speculation upon appointments or

\*L. to r.: Victor Cohn (seated), Harold M. Schmeck, Jr., Warren E. Leary, and author.





FIG. 5





FIG. 6

rifts in or among the Estates. After all governments can be dull without the hint of scandals.

This plaque (Fig. 7) was lovingly written by Wally Waterfall and your speaker, carefully edited by Phil Handler, and nailed to the "very door" at the present offices of the Institute of Medicine at the Watergate.

### *Epilogue*

Turning serious for an epilogue, I must acknowledge the deeper implications of a powerful government grown preoccupied with a maximum return on the health dollar. There are ominous features to the inexorable conversion of medicine to a public service system. As physicians of a particular kind, devoted to the academic and scientific side of medicine, we will have highly individual views of this transformation. At least one common feeling is regret at how slowly our caste has come to understand the forces of change and how late was our participation in the process.

The emergence of the Institute of Medicine, the rising tide of Academics flowing into the Fifth Estate, a growing sophistication among the

## SITE OF 'WATERGATE'

THROUGH THIS DOOR, IN THE EARLY MORNING OF JUNE 17, 1972, FIVE MEN GAINED UNLAWFUL ENTRANCE TO THE OFFICES THEN OCCUPIED BY THE DEMOCRATIC NATIONAL COMMITTEE AND WERE ARRESTED. THAT ACT GAVE THE SOBRIQUET "WATERGATE" TO A SERIES OF SUBSEQUENT DISCLOSURES THAT CULMINATED IN THE RESIGNATION FROM OFFICE OF PRESIDENT RICHARD M. NIXON ON AUGUST 9, 1974.

FIG. 7

consultants, more and wiser participation of physicians and scientists in the legislative and regulatory hearings—all these signify that future changes will not lack rational input from the experts-to-be-governed.

Those among you who are resolutely opposed to further change, and who feel powerless in the vicinity of the Medical Omphalos, are counseled to cling to other hopeful turns of the Federal process. For example, the Endangered Species Act of 1973 may conceivably be able to protect the most vulnerable relics of free-enterprise practice. But this is not the most important hint of relief.

There is a gathering suspicion that Congress, with its restless genius for experimenting with new remedies, may have self-inflicted another grievous wound to its powers and to those of the Second Estate. In 1969, with the innocent support of many of us who dearly love our planet, Congress passed the National Environmental Policy Act.

In essence, NEPA requires that all "major" Federal actions must first be examined to see if they will "affect" the environment. The law is somewhat bare of definition and is already overburdening the judicial calendar. Meanwhile, the Bureaucracies are to fill in slack schedules by constructing monumental Environmental Impact Statements.

Thus, even as we close this tour of the Federal City, one detects bemused concern in the Face of the Nation. The movement of the web of NEPA is charted daily as it draws about the temples of power. Does the Aesculapian merry-go-round perceptibly slow? Who knows? someday in Washington, as now at Delphi, only the scream of a lonely eagle may be heard.



RESEARCH, THE PUBLIC AND THE PRIVATE <sup>1/</sup>

by

Donald S. Fredrickson, M.D. <sup>2/</sup>

Good morning, ladies and gentlemen.

There are at least five good reasons why I am glad to be here on this Tenth Anniversary of the Roche Institute. For one, it has allowed me to travel here with Severo Ochoa who taught me something new about the regulation of protein synthesis through phosphorylation of an initiation factor. I have been for a week in Madrid with Severo and a small group of others who have been talking all day about science and the philosophy of science and up all night drinking beer with "Fitzi" Lynen. I don't know how Severo is doing now, but I am still in jet lag.

The second reason is that it allows me to visit with Sidney Udenfriend again and to have lunch, this time on him. Sid is now a member of my Advisory Committee; he comes in three times a year and has lunch in my office. Actually he pays for it; in fact, last time he disgracefully overpaid and left the change on the table. Because these are sensitive times, I want publicly to note here that the ten cents has been returned to the General Treasury.

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<sup>1/</sup> Presented on the occasion of the celebration of the Tenth Anniversary of the Roche Institute of Molecular Biology on May 20, 1977, in the Auditorium of Building 76, Nutley, New Jersey 07110.

<sup>2/</sup> Director, National Institutes of Health, Bethesda, Maryland.



The third reason has already been commented upon at great length this morning: the consanguinity of the little giant Roche and the big giant NIH. This Institute was formed by the Northern Hemorrhage--a somewhat smaller loss of Bethesda talent than the Great Southwestern Hemorrhage which formed the new Medical School in La Jolla; yet great quality offset the lesser volume. So many of those who left and others who are here today are certainly bound by common ties and memories. Like so many of you, I started in Building 3 in Bethesda. I remember clearly what it was like to be making an acetone powder in the cold room and have Arthur Kornberg come in. He had a way of looking at you for one minute that caused your technique and critical faculties to improve about a hundredfold. I, too, was one of those who had Jim Shannon as a spiritual father. It has often been said that Jim Shannon had an extraordinary talent for selecting people with great potential. One hears that comment most often from people who have been selected by him. I'm glad to add my note of homage to him today. I hope that Evelyn Attix, who also is here from the Heart Institute, will sit down with Earl Stadtman and other sources of institutional memory, and try to recollect all the names of the people who spent time in Building 3. They should be recorded on its walls.

Further reasons to come lie in the chance, now grown uncommon for me, to visit a few laboratories and to feel the pleasure attendant upon the celebration of good science. Arthur Kornberg has spoken of that today and all of us have resonated with that sentiment. Science is kind of a secular religion for those who have spent their lives at it; and by accident of appointment I am, for the moment, in the role of one of the archbishops.

As such I may be expected to have profound thoughts about science and its institutions. I hope you will bear with the substitution of a sentiment or two about this House, and about the universe of all such places existing for the purpose of scientific inquiry.

Roche, at its core, is private research. NIH is the world's single largest agency for public research. In the biomedical sciences, the public and private patronage of research has been interdependent for a long time. The relationship works both ways, even though it may seem unduly heavy on the public side. Today there are about 150 non-profit biomedical research institutions, or institutes, in the country that are not housed within academic institutions. Many are close to or in the shadows of universities and may have some affiliation. These are organizations that carry out research mainly for the sake of research as opposed to an adjunct to formal education. I asked the 37 members of the Association of Independent Research Institutes for an estimate of the support they were able to get from private funds for all kinds, including foundations and endowments. The mean figure is about 15 percent per year, and most of these institutes are heavily dependent on support from the NIH. In 1976, NIH put about \$190 million into contracts and grants to 140 such institutes. Some of those awards were quite considerable, the largest being more than \$20 million. Rare, indeed, then, is the institute like Roche, which does not depend on Federal support, yet is fully competitive in every measure of quality.

It is less than 40 years ago, when the situation was quite the other way around. Only about 6 percent of research support came from the government, more than half came from industry, and the rest came from private

foundations, endowments, and philanthropy. Thus, in the beginning, in this country, the support available to underpin biomedical research was nearly all private.

Of course, the research laboratory tradition is not really as old in this country as we would like to think. The Constitution and the Declaration of Independence are silent about science, except with respect to patients. Arthur mentioned Thomas Jefferson. Now Jefferson was the most intellectual of all the presidents and, as far as I know, one of the most oriented toward science. Yet it is interesting to read what Jefferson said about Harvey's great discovery. It seemed to him "a beautiful addition to our knowledge of the animal economy which, however, in some 150-180 years, had not had any very obvious influence on medicine itself."

When Pasteur and Koch were laying the foundations for bacteriology in Europe, experimental medicine in the United States hardly existed. One can gain a valuable perspective from reading Rene Dubos' book "The Professor, The Institute, and DNA." Dubos places this country's first experimental laboratory in medicine in an attic at Harvard on or about 1871. It was the comment of Professor Bigelow, who was the leading Professor of Medicine there at the time, that "the excellence of the practitioner depends far more upon good judgment than upon great learning . . . and we should not, for that reason, encourage the medical student to while away his time in the labyrinths of chemistry and physiology when he ought to be learning the difference between hernia and hydrocele . . ." If one had a hernia there was some truth in that, but it wasn't quite the talisman of the rational medicine that we hope to raise today.

Dubos says in his biography of Avery that medical research grew in this country because of the fortuitous coincidence of the germ theory of disease, the opportunity to put these theories into some practice and the fact that there was, in occasional families, a rising urge for social philanthropy. Many of you may know of our debt to a Baptist minister for the beginning of significant private support of medical research in America. The Reverend Fredric Gates was the philanthropic, as well as spiritual, advisor to one of America's richest men. At the turn of the century, he happened to read Osler's famous text on medicine--first published in 1892. Gates was appalled to find that, despite the great length of Osler's book, he could find only four diseases for which medical practice could pretend to have any cure. "When I laid down this book," he said, "I had begun to realize how woefully neglected in all civilized countries, and particularly in this one, has been the scientific study of medicine." Some years before, Flexner had said, "It became clear to me that medicine could hardly hope to become a science until it (medicine) should include endowed and qualified men who would give themselves to uninterrupted study and investigation, on ample salary, entirely independent of practice . . ."

Gates was a persuasive minister. It also helped, in a tragic sort of way, that John D. Rockefeller had recently lost his first grandchild from scarlet fever. In 1901 he set up the Rockefeller Institute for Medical Research and it was an example that was to inspire others to do the same. In fact, Zinsser wrote, in 1940, that no matter how anybody feels about



the origins of the great American fortunes of the 19th century, "one must acknowledge that the pre-eminent position of American medicine today"--which it began to occupy in the 1940s--"would have been impossible without a certain amount of rich malefaction in the 1880s and the 1890s."

Well, the story changed, of course, after World War II. You know what Vannevar Bush and the OSRD and others did in convincing the Congress that government ought to become seriously involved in stable support of medical research. By 1957 the government accounted for more than half of such support. Industry was supporting about 30 percent of biomedical research, most of it by pharmaceutical houses, and private sources had dropped down to about 17 percent. Since that time the percentage from private contributions has continued to drop. There is, nevertheless, still over \$250 million in private support, some of it in direct gifts, some of it from foundations--there are a few but not many left which support medical research--and also contributions from the 50 or so disease-oriented groups which solicit funds from individuals and corporations to support research upon matters of particular interest to them. Private contributions continue to grow but are not keeping up with the rate of inflation today--so we are sliding into a period when the Federal contribution is more and more important.

The pharmaceutical industry provides a large proportion of the total funds for support of biomedical R and D. It is a big contribution, something in the order of \$1,300 million annually. Industrial R and E is a very important segment of the total support.

Even though Federal support of biomedical research is now predominant and critical for the future of all institutions where new biomedical knowledge is a prime objective, there also remains a key role for private support of research in this country. The latter plays a complementary role to public support--indeed, an essential one--because it offers advantages over government support of research. First of all there is a certain flexibility. This may include the opportunity to support the young and off-beat person who cannot compete successfully in a peer review system that is focused on demonstrated ability and has limited uncommitted funds to venture as high risk capital each year. There is also need for local flexibility so institutions can have a measure of control over the direction and emphasis of its research activities. This cannot be achieved when all the essential decisions about what should be funded, and what not, are made in Bethesda on the basis of priority scores in a national competition. A proper degree of financial stability or long-range predictability is also very difficult to achieve on government funding based solely on single year appropriations. Private support, preferably in the form of endowments, offers this advantage.

In short, I believe that priorities in science should not be adjusted solely to the calendar of appropriations and the tastes of a single fiduciary like the Federal Government. A mix of private funding and public funding of laboratory research is necessary--particularly now that the government's expenditures for research are not in an expansive phase. During the past twenty years a partnership has been built up between the government and the academic and independent non-profit institutions in which biomedical

research is conducted. That partnership has proved to be effective and, I believe, mutually agreeable.

A less easy relationship exists between Federal support of research and for-profit firms engaged in research and development. There are some cogent reasons why that is so. Research directed with profit as a motive adds a value judgment or intent that has been known to tilt objectivity on occasion. The threat of conflict of interest unnerves government managers; the spectre of a loss of proprietary rights is no less threatening to industry. Yet the development of knowledge into new technology is an absolutely necessary route for converting to practical purposes the discoveries of research. Such translation is not something which government does well. It's rarely going to happen without capital investment, support that is predicated upon some kind of financial return. There are also some kinds of research for which profit makers are better prepared by virtue of staff, equipment, or organization. The government patrons of research have managed in recent years to come to terms with the uneasy problem of proprietary rights and patents devolving from publicly supported research. Public money is now also going to contractors who are carrying out research judged necessary to government research programs. We have recently decided at NIH that employees of profit making corporations should sit on advisory groups, including study sections; their membership, as with every other member, should be judged by the test of scientific competence alone. Although profit makers, as opposed to the non-profit institute or arrangement here at Roche, also seek the opportunity for their employees to receive grants for self-initiated research, I am not yet convinced of its feasibility.



There is a problem of cost-sharing with industry that is an awkward and difficult philosophical hurdle to overcome. I'm conscious of the problem seen by both sides in this debate--which continues, as it should.

A much more pressing problem, however, is how to create a more credible and acceptable partnership between government and industry in America to meet the requirements for full development of bio-technology. How can we appropriately use public money to provide not only seeds, but those more fully developed plants which private industry can grow into the fruits of research? And to do this while protecting both public and private interests at the same time? I'm not concerned here with questionable gadgets but useful and important technology--the biologics, the instruments, things for both research and medicine--upon which both new knowledge and the advancement of public health may depend. This requires a bridge of confidence that still has to be adequately constructed from both the public and the private ends. For the future of American enterprise in a competitive world, this good side of technology and partnership in development cannot be neglected. To the extent that we expect the present "revolution" in biology to continue, the partnership must be made to work.

A solution to this problem is complicated by the antipathy to some health technologies so widespread today. This is only one of the issues on the public and the private sides of research which have buffeted the institutions of science in the winds of the strong reform movements in which they find themselves today. The topic which I call "the public governance of science" has been very much on my mind of late. I noted Mr. Clark's



comments on the issue of recombinant DNA this morning. I agree with him. We do have to continue even in the present season of discontent.

Recombinant DNA research has given us a fascinating year in many ways. Not only are there the anxieties created by a new and ascending power of science, there has been the opportunity to savor the quality of debate about an important scientific issue--and to see how much scientists themselves have learned about the political process. Many scientists have abandoned a previous passivity, become politically wiser, and participated in increasing numbers during the past few months in the development of what will be one of the first laws regulating the use of an important basic research process. Some scientists, like other citizens, can be counted upon to tend the extremes of any political position. What has been so heartening recently is the sight of the "great silent middle," in motion at last, actively defending its legitimate interests.

There are some good sides to the issue of regulating research on recombinant DNA. There is emerging a new entente, perhaps still uneasy but absolutely essential, between "town" and "gown." There has to be public interest in as well as public understanding of what it is that we are trying to do and of the beneficial possibilities of the new techniques. Such debates will draw us all closer together in understanding.

We are in a period in which there is the dangerous possibility of over-reaction. Excessive central regulation can displace the "proximal governance," the self-discipline and self-regulation of institutions, which is the only practical way to enforce common standards. There is also the

prospect of an increasing cost of regulation of research which may drive some institutions away from the pursuit of knowledge in the laboratory. This is a grave danger.

Moraze, in his "Triumph of the Middle Classes," notes how Europe in the 1780s was characterized by "spirit," a word defined by Voltaire in his Dictionnaire Philosophique as "ingenious reason." One wonders today if ingenious reason has not been displaced by irrational fear. Yet in a place such as this, and on such an occasion, an embattled optimism is seen to survive. The strength and the hope and the possibilities of science need now only this further testimonial from me: "Happy Birthday, Roche Institute."

Remarks on Occasion of Receiving  
An Honorary Degree in Medicine  
From the Karolinska Institutet\*

by

Donald S. Fredrickson, M.D.\*\*

On behalf of the four members among the students today who were promoted de honoris causa, I should like to extend our deep appreciation to the rector, Professor Bergstrom, and to the faculty and student body of the Karolinska Institutet, for generously permitting us to share in the honors accorded our fellow students on this day.

These promotion exercises have been a reaffirmation of the now inseparable union between the arts of healing and the science base upon which rests a rational medicine. The essential unity of medicine and science was recognized much earlier in this distinguished institution--and certain of its European counterparts than it was acknowledged in my own country.

In the United States it was not until after 1910 that the profession of medicine was placed on trial and found guilty of quackery and excess empiricism. As a punishment, medicine was placed in the custody of science.

And together, the probationer and the trustee both prospered to the benefit of the patient. Especially since the 1940's

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\* In Stockholm, Sweden, on Tuesday, May 31, 1977.

\*\* Director, National Institutes of Health, Bethesda, Maryland 20014.

American medicine and biomedical research have effectively joined with the movement begun in Western Europe and Scandinavia.

The result of this international effort has been a virtual revolution in the understanding of the fundamental processes of biology. And application of this knowledge has dramatically improved the duration and quality of life for man and relieved much human suffering.

Because of these successes it is sometimes a shock to realize that today medicine and the technology that is spawned by science are again the subject of criticism, particularly by government. This time the movement for reform comes from the mounting strain that health care places on the public purse. The biomedical sciences, too, are not immune from concerns about the directions taken by the search for new knowledge, and particularly about how effectively information is processed and resynthesized for practical benefit.

In these times, then, the biomedical sciences are undergoing both external and self-re-examination. The results, I believe, provide both reassurance and new responsibilities to the partnership between science and society.

It is clear that, provided sufficient stable support, the understanding of the nature of life and of man will continue to grow at an accelerated and exciting pace.



At the same time, it is also clear that the practical application of the new knowledge to come will be very demanding. The validity of new interventions in medicine will require greater time and patience. Greater sources of information about populations will have to be acquired. Preventions must be stressed over cures. The benefits of appropriate new technology must be made fairly available to all, including those developing parts of the world who have yet to acquire sufficient scientific capability of their own.

The maintenance of the balance between the objective and the compassionate sides of medicine will place greater responsibilities upon all of us than in the past. But to mankind the rewards of future achievements can still be greater.

Finally, I cannot speak personally of what this occasion has meant to Dr. Bjuggren, Director-General Mahler, or Dr. Perlmann.

For myself, I confess it has been most revealing. I have discovered at least one part of me which is primarily covered by that half of my genes which are Swedish. I am sure it is my heart. This evening it seems to be beating with a proud ancestral rhythm. On behalf of those family roots of mine transplanted years ago from Sinaland, I would like to thank you for the occasion of this reunion.

# THE BANNING OF SACCHARIN, 1977

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HEARING  
BEFORE THE  
SUBCOMMITTEE ON  
HEALTH AND SCIENTIFIC RESEARCH  
OF THE  
COMMITTEE ON HUMAN RESOURCES  
UNITED STATES SENATE  
NINETY-FIFTH CONGRESS  
FIRST SESSION  
ON  
EXAMINATION OF THE RISKS INCLUDED IN THE USE OF  
SACCHARIN AND THE DECISION BY THE FOOD AND DRUG  
ADMINISTRATION TO BAN THE SUBSTANCE FROM THE  
MARKET

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JUNE 7, 1977



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(II)

# CONTENTS

## CHRONOLOGICAL LIST OF WITNESSES

TUESDAY, JUNE 7, 1977

	Page
Hayakawa, Hon. S. I., a U.S. Senator from the State of California.....	4
Robbins, Frederick C., M.D., dean, medical school, Case Western Reserve University; John J. Burns, Ph. D., vice president, research, Hoffman-La-roche, Inc.; Joyce C. McCann, Ph. D., senior fellow, American Cancer Society, University of California (Berkeley); Abraham E. Nizel, D.M.D., professor, Department of Oral Health Services, Tufts University; John A. Oates, M.D., professor, Department of Pharmacology, Vanderbilt University School of Medicine; Albert J. Stunkard, M.D., professor, Department of Psychiatry, Philadelphia General Hospital.....	8
Frederickson, Donald S., M.D., Director, National Institutes of Health, accompanied by Dr. Guy Newell, Acting Director, National Cancer Institute; and Dr. Marvin Schneiderman, Associate Director, Division of Cancer Cause and Prevention.....	91
Kennedy, Donald, Commissioner, Food and Drug Administration.....	97

## STATEMENTS

Case Western Reserve University, Frederick C. Robbins, M.D., dean, medical school, prepared statement.....	36
Frederickson, Donald S., M.D., Director, National Institutes of Health, accompanied by Dr. Guy Newell, Acting Director, National Cancer Institute; and Dr. Marvin Schneiderman, Associate Director, Division of Cancer Cause and Prevention.....	91 ✓
Hayakawa, Hon. S. I., a U.S. Senator from the State of California.....	4
Hoffman-La Roche, Inc., John J. Burns, vice president, prepared statement.....	60
Kennedy, Donald, Commissioner, Food and Drug Administration.....	97
Prepared statement.....	124
Office of Technology Assessment, saccharin panel, Joyce McCann, M.D., member, prepared statement.....	64
Robbins, Frederick C., M.D., dean, medical school, Case Western Reserve University; John J. Burns, Ph. D., vice president, research, Hoffman Laroche, Inc.; Joyce C. McCann, Ph. D., senior fellow, American Cancer Society, University of California (Berkeley); Abraham E. Nizel, D.M.D., Professor, Department of Oral Health Services, Tufts University; John A. Oates, M.D., professor, Department of Pharmacology, Vanderbilt University School of Medicine; Albert J. Stunkard, M.D., professor, Department of Psychiatry, Philadelphia General Hospital.....	8
Prepared statement.....	36
Tufts University, Department of Oral Health Services, Abraham E. Nizel, D.M.D., professor, prepared statement.....	70
University of Pennsylvania, Department of Psychiatry, Albert J. Stunkard, M.D., professor, prepared statement.....	83
Vanderbilt University School of Medicine, Department of Pharmacology, John A. Oates, M.D., prepared statement.....	77

(III)



STATEMENT OF DONALD S. FREDRICKSON, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH, ACCOMPANIED BY DR. GUY NEWELL, ACTING DIRECTOR, NATIONAL CANCER INSTITUTE, AND DR. MARVIN SCHNEIDERMAN, ASSOCIATE DIRECTOR, DIVISION OF CANCER CAUSE AND PREVENTION

Dr. FREDRICKSON. Thank you very much, Mr. Chairman. I have a very brief statement, and if you have no objection, I would like to read it.

Senator KENNEDY. Fine.

Dr. FREDRICKSON. As Director of the National Institutes of Health, I have been requested to appear before the committee today to comment upon the scientific evidence that saccharin may cause cancer in man. The committee has received today the report of an OTA study of this question. It is also considering what public action should be taken on the basis of this information and the action of the FDA.

I am not a specialist in carcinogenesis, but I am accompanied by two experts from the National Cancer Institute, Dr. Guy Newell on my left, who is the Acting Director of the Institute, and Dr. Marvin Schneiderman, who is Associate Director for Field Studies and Statistics, Division of Cancer Cause and Prevention.

The scientific evidence indicates that saccharin is a carcinogen. So far, this has been demonstrated in animals. Proof does not exist that this is true in man. From experience, however, one must assume that, until proven otherwise, materials shown to cause cancer in animals also cause it in human beings.

It will be extremely difficult to prove that saccharin is an exception to this rule. When the animal data are carried over to man in the conventional way, they indicate that 2 to 3 percent of the 30,000 new cases of bladder cancer each year could be due to saccharin in the low doses now used by the American population. Such a contribution to bladder cancer by saccharin cannot be detected unequivocally; nor can it be ruled out by any known methods for studying human populations.

Mr. Chairman, my colleagues and I will be very glad to respond to any further questions you may have.

Senator KENNEDY. Well, now, if we could get to the issue about the nature of the risk, and who is really going to assume that. How do you assess the risk, Dr. Fredrickson and the other panelists, in terms of the utilization of saccharin, in how much danger the American population faces if it does not have that kind of a ban? How does it relate to other kinds of choices which the American population makes daily, in terms of smoking, flying airplanes, using other toxic substances, driving, other factors, and how would you assess it?

Dr. FREDRICKSON. Well, again, always speaking for the general population, Mr. Chairman, saccharin appears to be a weak carcinogen, as you have already heard this morning. Relative to cigarettes it would probably have to be considered on the basis of animal tests about one-tenth as powerful, or as dangerous a carcinogen.

Nevertheless I think, as my statement indicated, and as I believe, there is a finite risk of it causing an excess of cancer in those individuals that have been exposed to saccharin. One of the great problems with the population data upon which such estimates are based is that if we know there is a risk of a substance causing human cancer, one can also consider with a high degree of probability that there will be differences among individuals, that there may be a sub-set of the human population who will be highly resistant to such carcinogenic action, but just as likely there may be a sub-set of individuals who may be much more sensitive to that.

Senator KENNEDY. But even within that frame of reference, even assuming that there is a more vulnerable segment of the population, looking at Dr. Newell's testimony before the House committee where he indicated that, looking at the most extreme case, your extrapolations may get a four one-hundredths-of-1-percent increase in terms of bladder cancer for the individual, which comes anywhere from 300 to 400, looking in terms of population. We are looking at three-one-hundredths to four one-hundredths of 1 percent. In terms of the individual, it is extremely remote; in terms of the population, we are looking to 300 to 400 a year.

When you relate that to other kinds of choices, or questions that the population is making with a much higher degree—we know, for example, that the incidence of airline crashes is a good deal more than that, let alone automobile or other factors—alcoholism, and other factors—and yet, we permit individuals to make choices on these. So, we are talking about, as I understand it, a relatively light risk in this.

Dr. FREDRICKSON. It is true, Mr. Chairman, that there are other activities in which humans engage, where they make a choice, and which carry something of a higher risk, there is no question about that. The matter then evolves to the value of one human life, or a few, and the question of what choices Government must make and what people must be allowed to retain for themselves.

Senator KENNEDY. Well, that is exactly right, that is the policy issue. This comes down to the question as to whether that particular choice is an issue in which individuals can make a conscious decision in terms of utilization, as compared to water, air, smoke pollution, and what should be the burden of the regulatory process in terms of this, let alone an individual, with whatever notification and information they can make.

Dr. FREDRICKSON. Yes, I agree, that is the very problem before us.

Senator KENNEDY. And you come out in favor of the Food and Drug Administration on this.

Dr. FREDRICKSON. Well, Mr. Chairman, fortunately you have already heard ample evidence that there is no unanimous opinion from science, so, I am relieved of the presumption of presenting one. [Laughter.]

My own personal view is that it would be in the best public interest to limit, if possible, the exposure to saccharin, which is now almost ubiquitous as an exposure in man. And in that sense, given that the Food and Drug Administration has elected—perhaps has had no choice in a portion of its decision—to ban it as a food additive, and to examine whether or not it should be retained as something that is available over the counter, is a set of actions with which I am in agreement.

Senator KENNEDY. Why do you think it is so overwhelming among the American people that they feel on this issue that they want to make a choice and decision? When they had the Red Dye No. 2, there was not even a ripple, with the exception of some of the particular interests—there was hardly a ripple. Why is there such a sense and a feeling, do you think, on this? Do you think it is just the industry pressure? There is no question that is a substantial part of it.

Dr. FREDRICKSON. Well, I suppose that must be part of it, Mr. Chairman. I would also guess that there are a number of reasons, probably real anxieties on the part of certain people, those who have diabetes, who have certain other diseases, where they have a feeling it is extremely important in maintaining their adaptation. I would guess that there is a whole list of other items one might develop the same reaction because it does represent a matter of choice; and probably there is also that added element of uncertainty on the part of the public of just how risky saccharin is. There has been such a lengthy debate about it that not everybody can find a source of ready agreement as to the risk that is really represented.

Senator KENNEDY. Senator Schweiker?

Senator SCHWEIKER. Thank you, Mr. Chairman.

Doctor, following up on the chairman's earlier question, can we somehow delineate the risk so that people will have some guidance in making decisions? People every day decide how big a risk they are willing to take, letting their kids play football; or driving automobiles despite the risk of accidents; or flying private planes, which have a much worse accident record than commercial airliners. What is the risk from saccharin use in perspective?

Dr. FREDRICKSON. Well, I think part of that perspective, Senator Schweiker, should be the degree of discretion that actually is afforded the individual. You have heard testimony this morning about the fact that a large portion of the population exposed to saccharin is actually a population of children. Further questions were raised by the committee about the discretion of parents—

Senator SCHWEIKER. Let me say, don't most children drink sugar-sweetened soft drinks, not diet soft drinks? I mean, let's put that on the table. And sugar consumption poses some important risks and it increases your likelihood of developing diabetes, cavities, obesity, and heart disease. Is not the risk there, no matter what you do? It might



not be worth fighting to keep one alternative saccharin-sweetened drinks off the market, when the other alternative sugar-sweetened drinks, also poses a risk. You may not be running a risk of cancer, but you're still running some risk.

Dr. FREDRICKSON. I cannot answer the first part of your question, Senator, I do not know what the distribution of purchases is of 9-year-olds, as opposed to 14- or 16-year-olds, I do not know. There are perhaps some risks of sugar. I think this is a poor place to debate them, relative to the diseases you mentioned. I think the question of dental caries is not one that is debatable; I think it is with respect to diabetes and all the other diseases that have been attributed to sugar. There is still no risk of cancer from sugar, however, so far as we know.

Senator SCHWEIKER. How much of a risk is there from eating sodium nitrite? I would like to ask you cancer specialists that. How much of a risk do we face from sodium nitrite on your breakfast tables today?

Dr. FREDRICKSON. I demonstrated my wisdom, bringing my experts today. Do you know, Dr. Schneiderman?

Dr. SCHNEIDERMAN. No.

Senator SCHWEIKER. Well, I have here an article from the Washington Star. The headline reads: "Panel Okays Use of Nitrite Despite Warning." The story goes on to say that the panel, which began its study in February 1975, conceded there is evidence that a chemical formed from nitrite may have cancer-producing properties \* \* \* the cancer-causing properties of a chemical formed from nitrite "cannot be ignored."

Now, surely, you know something about this. I mean, this is your department, this is cancer. They put nitrites in bacon, and we eat it for breakfast. I would like to know what our position is on sodium nitrite being added to foods.

Dr. SCHNEIDERMAN. It seems to us, looking at sodium nitrite, and other materials which are used to make our food supply last on the shelves longer and make it cheaper for us, that these materials apparently do not operate as carcinogens all by themselves. Sodium nitrite itself has to combine with other materials to produce the nitrosamines and the things that in the animal tests have been shown to be the carcinogens. I do not believe that sodium nitrite has been shown to be a carcinogen.

There is also some evidence that some things in our diets actually serve to suppress this interaction effect. So, sodium nitrite in the presence of the other things in the American diet may not be a carcinogen. This is an area in which we have to do a lot of work, and I think the Department of Agriculture panel which made the decision to recommend continued use of sodium nitrite came to that conclusion because of this other information around sodium nitrite.

Senator SCHWEIKER. The article goes on to say:

Studies have found that nitrites used in curing meat can combine with other substances to form a nitrosamine that is among the most potent cancer-causing agents known. The report noted that the principal cancer problem is with bacon that is fried quickly. But it said the amount of cancer-producing agent caused by such frying, or in the consumer's digestive tract is so small that the effects of such levels on either humans or animals are not yet known.



Now, here we are allowing, by our own admission, something that can lead to cancer to be put in human food. It's done every day in the week, as easy as bacon and eggs. I just have trouble reconciling our approach to the nitrite case with what you folks are recommending on saccharin. Does not the body metabolize sodium nitrite into a cancer-causing substance, or is this panel of scientists from the Agriculture Department wrong?

Dr. FREDRICKSON. I think at the current state of knowledge, Senator Schweiker, we have to agree that there is a suggestion that nitrites might cause cancer. But we cannot, for example, give you today any assessment of relative risk of the nitrites in bacon, as opposed to saccharin.

Senator SCHWEIKER. They are among the most potent cancer-causing agents known to man. Dr. Fredrickson.

Dr. FREDRICKSON. The nitrosamines are, Senator Schweiker, which may be derived from nitrites.

Senator SCHWEIKER. That happens in the human digestive system, does it not? That's what this article says. Doesn't this represent a danger, that we should be worried about? Everybody eats bacon and eggs in the morning, and here is one of the most potent cancer-causing agents known to man, and we still eat bacon for breakfast, and nobody gets excited about it.

I have trouble with what our priorities seem to be here. Every panelist here said saccharin was low risk, a very weak carcinogen. Here is one of the highest risk carcinogens, and we are still putting it in bacon, and selling it, and people eat it every morning for breakfast.

Now, what is the hypocrisy here, what are we doing? It is a food additive question, surely.

Dr. FREDRICKSON. Yes; it is, Senator Schweiker. It is added to prevent another disease from which man suffers, and that will be part of any assessment of relative benefits.

Senator SCHWEIKER. It prevents another disease? Well, now, wait 1 minute—wait 1 minute. That sounds like you're weighing risks and benefits. I thought you folks said the Delaney clause never allowed a weighing of benefits versus risks. If I heard one thing from FDA and NIH it was that we could not weigh risks and benefits when food additives could be shown to cause cancer, I have trouble understanding what the difference is with nitrites, that Federal food additive safety policy allows us to measure benefits against risks in this case.

Dr. FREDRICKSON. I am not sure that any decision about nitrite has taken into account the benefits because what you say about this aspect of the food additive law and Delaney in particular is true, Senator.

Senator SCHWEIKER. Well, I will reserve most of my questions in this area for the Food and Drug Administration, but I did want to bring up the nitrite issue.

Another interesting point that I would like to pursue relates to the impurities in saccharin. I heard the panelists this morning say that the only real culprits that they have been able to nail down in short-term tests were the impurities, the 20 parts-per-million impurities. We are faced with the question of whether the real trouble is with pure saccharin, which has been negative in all the short-term tests, or with the impurities.

Can you enlighten us at all as to what are the eight impurities that we have identified? Apparently we have not yet identified 12, but we have identified 8. Do you have any information about those eight that have been identified?

Dr. FREDRICKSON. It is our impression that none of those impurities have been identified, Senator Schweiker, we do not know what they are, any of them.

Senator SCHWEIKER. Is it fair to say that the trouble could either lie in pure saccharin, or in its impurities, then?

Dr. FREDRICKSON. I think it has not been excluded that a contaminant of commercial saccharin, which is used in all the products at interest here, could be the carcinogen; that is quite possible. That has not been excluded.

Senator SCHWEIKER. That is all I have, Mr. Chairman, thank you.

Senator KENNEDY. Senator Nelson?

Senator NELSON. I understand from the Food and Drug Administration that in the Canadian tests there were no contaminants. Is that correct?

Dr. FREDRICKSON. I believe they used the most purified saccharin that they could obtain. I do not know that there was a basis for assuming no contaminants, Senator.

Senator NELSON. I understood that previous tests on saccharin did not separate out the impurity, OTS (o-toluenesulfonamide). Now, I understand the Canadian tests were done with the contaminants alone and with pure saccharin, and the pure saccharin caused cancer in animals. Is it correct, or incorrect that saccharin caused cancer in animals, and the contaminant did not. Did I misread that?

Dr. SCHNEIDERMAN. The Canadian tests were specifically designed to test the question of whether the carcinogen was the contaminant, or the saccharin per se. The Canadians then used the most purified saccharin that had been developed and was available to them. This purified material is what the animals in Canada were tested with, and which eventually led to the increase in the bladder cancers in both first and second generation animals. The tests they conducted on the suspected contaminants did not show any cancer-causing effect.

Senator NELSON. Who did those tests?

Dr. SCHNEIDERMAN. The Canadians.

Senator NELSON. And the contaminant test did not disclose any tumors, and the saccharin test did.

Dr. SCHNEIDERMAN. The known contaminant did not. The Canadian material was then further examined, and, as Dr. McCann indicated earlier, about 20 parts per million of the Canadian material was found to be not saccharin but still some other contaminant. In testing a concentrated form of this 20 parts per million stuff in her mutagenicity tests she found this material was mutagenic; while now testing the doubly purified saccharin, she did not find that the saccharin led to mutations in her tests.

Senator NELSON. There were mutations or tumors?

Dr. SCHNEIDERMAN. Mutations. These are the bacteria tests for mutations.

Senator NELSON. In looking at some of the studies of saccharin. I note that scientists simply say that saccharin is not of any known health value to diabetics or fat people.

I looked at some diet tests on rats and humans. The rats that had saccharin are more than those that did not. Then there was a controlled study by the Harvard School of Public Health and the Peter Bent Brigham Hospital, Boston, involving 247 obese individuals and 100 diabetic persons, in which no significant difference was apparent when the weight loss of users and nonusers of low-calorie diet foods was compared (Journal of American Diet Association, 23, 327-330, 1954). FDA Papers, October 1969, reported that "none of the few controlled studies reported to date have established a useful role for non-nutritive sweeteners as weight-reducing aids except under the most carefully controlled conditions."

Are there any conclusive tests that have been done, that demonstrate an important need for saccharin for diabetics, overweight, or heart patients? None have come to my attention.

Dr. FREDRICKSON. The answer is no, Senator Nelson. There is no test that is available that demonstrates a specific need for saccharin by such patients.

Senator NELSON. So, what we are dealing with here is a risk with no known benefits. Is that correct?

Dr. FREDRICKSON. I would not go so far as to say "no known benefits" because that goes off into regions of even aesthetics.

Senator NELSON. All right, with no tests demonstrating benefits, conclusively, to diabetics, overweight, or heart patients.

Dr. FREDRICKSON. That is correct.

Senator KENNEDY. Thank you very much.

Dr. FREDRICKSON. Thank you.

Senator KENNEDY. The committee will be in order.

I want to welcome you, Mr. Commissioner. I think this is the first time you have been before the committee since the time of your confirmation—this is a nice issue for you to start out with.

We are very, very fortunate, I believe, to have you in the important position of Commissioner of the Food and Drug Administration at this time. Those of use who know of your record know of the excellence of your work as a biologist, researcher, as well as an administrator. We are aware of the openness with which you approached this particular job, and the challenge which the FDA presents, and the leadership that you are providing.

We are delighted to welcome you here before the committee and look forward to your testimony.

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20014

STATEMENT BY

DONALD S. FREDRICKSON, M.D.

DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ON

ENVIRONMENTAL HEALTH SCIENCE

BEFORE THE

SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH

COMMITTEE ON HUMAN RESOURCES

UNITED STATES SENATE

Friday, June 10, 1977



Mr. Chairman and Members of the Committee:

It is a pleasure to meet with the Committee this morning to discuss activities of the National Institutes of Health that contribute to the understanding of man's environment and its effects on health. Particularly, I should like to speak of the role of our National Institute of Environmental Health Sciences (NIEHS) and how that organization relates to other components of NIH and the Federal Government with major interest in environmental health problems.

It is now well recognized that health and disease result from the interaction between intrinsic biological processes and extrinsic factors impinging upon these. The intrinsic nature of man is largely determined by his genes. The extrinsic factors include his physical environment and the cultural and social conditions to which an individual is exposed.

Virtually every biological process and most diseases require careful attention to extrinsic factors. And every Institute of NIH is intimately concerned with environmental influences upon its assigned subject of research. As the knowledge of these influences has expanded, it has become apparent that the chemical and physical forces in the environment which determine health are numerous and very poorly understood. Thus, a collective study of these forces--not limited to a single disease or biological system--has been dictated. This is environmental health science.

Its tasks are to identify those substances or forces in the environment that threaten health. They must be measured precisely and classified so that useful generalizations can be drawn about the mechanisms

whereby they may adversely affect the body. Finally, this must lead to establishment of safe exposure levels, steps to offset toxicity when these levels are exceeded, and ultimately the minimizing of opportunity for such excesses in exposure.

The National Institute of Environmental Health Sciences has been established to engage the first several of these tasks, relating mainly to the production of new knowledge. Besides feeding its findings into the disease-oriented programs, the Institute also works closely with the regulatory agencies that must apply that knowledge to testing, standards-setting, and preventive actions. Interaction between NIEHS and the several categorical Institutes is paramount in maintaining its scientific base. Its close relationship with regulatory agencies such as FDA, CDC, EPA, and the Consumer Product Safety Commission are critical to its perception of how the new knowledge must be extended into the practical realms of standard-setting and regulation.

The scientific activities of the regulatory agencies, in turn, must be attuned to their responsibilities, yet must so overlap with the work of the primary research agencies that regulations are based on sound scientific principles.

One cannot escape plural approaches nor expect to eliminate some redundancy in the environmental research done by different agencies. The field is still inadequately developed and yet already so broad that a monolithic approach, attempting to combine long-range goals with immediate problem-solving in a single agency, would be counterproductive.

Nevertheless, there is rapidly emerging an undeniable need for continued improvement in coordination of environmental research within departments and agencies and above them, as is stressed in the President's Environmental Message. Coordination within NIH is certainly not yet ideal.

We are striving to improve it and are considering new mechanisms for doing so. For example, we are looking at carcinogenesis--a troublesome field due to the multiplicity of known and possible environmental causes of cancer, the increasing demand for tests of more compounds and by more efficient methods, and the multiple requirements of numerous agencies for such results.

I would like to mention an area of special interest crossing three Institutes of NIH--namely, NIEHS, NCI, and the National Institute of Child Health and Human Development (NICHD). These Institutes are engaged in effective interagency coordination immediately related to environmental health hazards to fetuses and infants, and ultimately to the more effective control of these hazards.

NIEHS conducts and supports research on the toxicology of a range of chemicals on the developing organism and on reproduction. The studies include the pharmacologic action of various agents in young or under-developed animals, and basic alterations of genetic material which may contribute to cell mutations and birth defects. There are 14 intramural research projects and 35 active research grants, at a total funding level of \$2,082,000. In addition, 13 environmental health science centers and program projects are involved in directly related research, at a current funding level of \$1,237,000.

NICHD is interested in the prevention and treatment of all diseases and disorders of pregnancy and the newborn. Here, interest centers upon human development as affected by environmental agents (whereas NIEHS focuses on the effects of a wide range of agents on the human body, including its development). NICHD currently supports 100 projects at a



funding level of \$9.9 million to investigate hazards in fetal and infant environment. Basic and applied research on the cause of these disorders will benefit from the research findings of other Institutes studying environmental factors. NICHD will also continue to emphasize studies leading to a better understanding of environmental influences that impede and alter normal growth and development in the fetus and child.

NCI has our largest single investment in research on environmental carcinogenesis. In the area of childhood disease, NCI's interest parallels that of the above Institutes, but the focus is on children's cancers caused by environmental agents. Much of NCI's research is yielding results that increase our understanding of the cause, prevention, and treatment of cancer in the young child.

Between the departments and the agencies, the initial method of coordination was exchange of information. This is gradually being supplanted by appropriate division of labor, which minimizes unnecessary duplication, capitalizes upon the special expertise and resources of the different agencies, and hastens the closure of gaps in essential knowledge. Better methods are evolving for the allocation and pooling of effort.

NIH sponsors a number of other coordinating efforts. NCI has established the Interagency Collaborative Group on Environmental Carcinogenesis and the Clearinghouse on Environmental Carcinogenesis. These ensure mutual exchange of findings and preclude unproductive duplication. NIEHS hosts a continuing series of conferences on current problems in environmental health. The first, held in 1971, dealt with the polychlorinated biphenyls (PCBs). The most recent, held last month, considered vinyl chloride and related compounds. These have provided a valuable opportunity for the regulatory agencies, the regulated industries, and



academic scientists to assess the state-of-the-art and plan future research.

One of the more important avenues to the environmental causation of health problems is epidemiology--the study of the incidence of disease in attempts to identify causes. I have established in my immediate office a focus for coordinating and encouraging this fact-finding effort. This will permit us to husband scarce resources, to foster maximum use of the National Center for Health Statistics, and to be sure that data we collect about diseases and possible environmental causes will be made available to all concerned parties, including EPA.

It is important that the agencies retain tactical responsibility for their separate programs. For example, agencies primarily serving health practice may need to know precisely how toxic agents enter the body, or disease control agencies must perfect the technology for surveillance. At NIH, day-to-day program responsibility is vested in the cognizant Institutes and programs, with a view to encouraging speed and ingenuity in problem-solving.

I am convinced of the need to separate the more basic and long-term research from regulation. I am equally certain that the interface between these activities must provide close exchange. Coordination of environmental health science within the Public Health Service, especially among the NIH, the National Center for Health Statistics, the Food and Drug Administration, and the Center for Disease Control, is effected through a number of mechanisms.

Foremost among these is the DHEW Committee to Coordinate Toxicology and Related Programs, established in 1973 and chaired by Dr. Rall, Director of NIEHS. The Committee provides a focus for coordination

within HEW and, by inviting EPA and other regulatory agencies to participate fully as observers, ensures the sharing of information and concerns throughout the Government. This, to my knowledge, is the only chartered and continuing broad-based coordinating effort. A recent product of the Committee, a white paper on testing chemicals for mutagenic activity, had its inception in an EPA request for information to aid in standard-setting. The current knowledge brought together in this report will be useful to the academic research community, regulatory agencies, and industry.

We have recently received the Report of the Second Task Force for Research Planning in Environmental Health Science, which identifies national needs over the next five to eight years. Participants came from a large number of Federal agencies, as well as from the academic and industrial communities, and the report provides a valuable starting place for setting priorities over the next few years.

I appreciate the opportunity to share this position with the Committee. I will be glad to answer any questions.

TALK BY  
DR. DONALD FREDRICKSON  
DIRECTOR, NATIONAL INSTITUTES OF HEALTH  
AT THE  
CLAUDE BERNARD SCIENCE JOURNALISM  
AWARDS LUNCHEON  
NATIONAL SOCIETY FOR MEDICAL RESEARCH  
JUNE 17, 1977

What Ted Sherburne said at the last luncheon ought to be repeated. He said: "At no time has the importance of communicating science to the public been greater." Well, at no time, that is, until now. It is even more important now and what he could have added is that this town probably has the greatest importance of all in the scientific enterprise. That's because Washington has become the Omphalos of medicine and of the science that forms its rational base.

Let me explain what I mean by what I just said. I have had occasion to think and talk about this matter before. Some months ago I heard a lecture by a very distinguished earth scientist, Frank Press, who is a marvelous authority on plate tectonics. He gives a lecture accompanied by time-lapse photography which shows you in four minutes how all the continents shuttled around through millions of years and eventually formed today's map. That got me thinking. After the whole thing cooled down, particularly in the Peloponesus, the Greeks decided to establish the center of the earth and they put it at Delphi. They called that the Omphalos and it was the medical Omphalos, too.

Sometime after making that astute connection, I went to Brown University-at Providence, and told them about what had happened to the medical Omphalos. You know, it had gone from Delphi to Padua, to Leyden, to Vienna, to Edinburgh--and finally it crossed the ocean. It got to Johns Hopkins, went up to Boston sometime later, and then it may even have got out as far as Minnesota where the Mayo Clinic is. But with the Hill-Burton and the NIH grants, everybody became so equally sophisticated that the Omphalos disappeared.

But then, after Hill-Burton, came the heart-cancer-and-stroke legislation, Medicare-Medicaid and the catastrophic illness amendment, health planning and resources legislation, the health manpower bill--and the end is not in sight: a Clinical Laboratories bill, a cost containment bill, the recombinant DNA bill and so forth are still to come. There isn't any question that the Omphalos is back in business and this time it's in Washington, D.C., probably for good. Well, if not for good, at least for keeps!

Now anybody brought up on the taxonomy of Linnaeus (which I was, of course, being half Swede and having had to study it) can't think about Washington more than a few minutes without breaking it down into its component phyllums. Everybody knows that there were three principle estates in the time of Louis XVI: the nobles, the clergy and the people. But that has obviously been changed--if one looks at Washington from the medical scientist's point of view. Although the President is annually certified by U.S. News and World Report to be the most important and influential person in the government, the Administration and its elected and appointed officials are really the second estate, because, in relation



to medicine, it's the Congress that first discovered the vulnerable soft spots in the health-care system, has consistently fostered public patronage of science, and has been both proposing as well as disposing for a number of years--at least until the present Administration came along. I guess Federal judiciary has to be the third estate--it is still in its infancy but I suspect that it is going to have a tremendous maturity in regard to the regulation of science and of medicine.

Just to complete the picture let me skip to the fifth estate--a sort of proletariat which has three components. There are the staffs, particularly of the Congress; they are indispensable and they're innumerable and they're non-tenured. Then there are the bureaucrats who are highly tenured, equally indispensable and enumerated annually by the OMB. Then finally, there are the lobbies which tend to be made up of those who are displaced from the other estates but whose compensation makes up for the sacrifices that they have had to bear.

Then there is the one estate that hasn't changed since the day that Edmund Burke declaimed "There were three estates in Parliament, but in the Reporters Gallery there sat the Fourth Estate, far more important than all the rest." Now of course that has not been everybody's view of the press. Thomas Jefferson, a great intellectual, said, "I do not take a single newspaper, nor read one a month, and I feel myself infinitely happier for it." Sir James Barry took a more balanced view; he said: "The press is either the greatest blessing or the greatest curse of modern times, one sometimes forgets which." Well, actually, of course, it's both. It depends on which side you're sitting.

It is very easy to understand why a politician like Jefferson found it distasteful to read the newspapers. It is not the job of the press to make politicians happy, although sometimes politicians work very hard to make the press happy. If the political process in Washington is--and it certainly is--delicately adjusted to the appetite and the digestive rhythms of the press, I think this is really as it should be, for there isn't any other force to guard the interests of the governed--except us in science. But our method is so dull that we can't compete with the job that you're doing. You're the ones. The Fourth Estate has to draw the balance sheet on how well the rest of the estates are doing their job.

In short, you've got to do the sort of job that Cris Russell has done so thoroughly on her series which brings her to the table of honor today. I don't think it was her intention to make everybody happy, and she didn't. But there are very few who would seriously deny that she really served a useful public purpose, and that the problems, the difficulties and the contradictions that she has so meticulously laid out are matters of important public concern. Her conscientious effort to inform and to present both sides of each argument really did a service to all of us.

Washington is unusually fortunate. It has, in addition to the Congressional Record, three daily newspapers though one of them is still printed in New York for sentimental reasons. Actually, there may shortly be a fourth: I noticed that the coin-operated newspaper dispenser in the Rayburn Building now include one for the Atlanta Constitution.

I think that in journalism, like auto racing, not all vehicles are the same. I'm not going to praise those people who work for Science or for Nature; they have similar problems, but they have reasonable relief

from the tremendous commercial competition for space and time--a problem which seems to have made commercial TV incapable of coping with the requirements of science reporting. I'm afraid I've given up.

The newspapers do a much better job but they are a really tough medium in which to achieve a demonstration of the skills of a careful observer and a gifted writer. This is a fact not much appreciated by scientists who willingly submit their wares to an editorial board and accept ruthless comment on their content but who would rebel completely at the tyranny of any rewrite person or the editors who might change the content or limit the space. Now that is an obstacle course that has to be accepted as a job requirement by a reporter.

I think it takes exceptional talents--and certainly not a little grace--to score a triumph in reporting on the substance of science and medicine rather than on its petty scandals. And something has to be said for Barbara Cohen, too. It also takes a helpful editor who recognizes that public understanding of scientific problems is a prerequisite for a rational and effective public policy. We can be very grateful to her for turning Cris loose and for giving her some 500 column inches to tell her story.

Now, I've got a minor presentation of my own for you, Cris, but first I must deliver a message. I had a call just before I came from a person whose calls I always take--not my wife but someone else--and I was asked to read this brief statement. It goes:

Because Cristine Russell is a special friend, I am personally pleased beyond measure that the National Society for Medical Research is honoring her today with the esteemed Claude Bernard Award for Scientific Journalism.

Beyond that personal pleasure, I want to join the National Society on behalf of the Department of Health, Education, and Welfare in recognizing the brilliant journalistic study of environmental cancer that Cristine Russell authored in 1976. Her searching discussion of exceedingly complex scientific and medical information, and probing discussion of the government research and regulatory programs to protect the public from cancer causing chemicals, made the distinctive contribution to public enlightenment that you are honoring today.

At least as significant, Cris' series also spurred a reexamination that continues even now by scientists, legislators, and administrators as to whether we in government are doing all we can to define and control environmental threats to health and life itself.

Cristine Russell's series is a superb example of journalism at its best--probing, critical in the finest sense, enlightening the public, and influential in moving both students and shapers of public policy.

Joseph A. Califano, Jr.  
Secretary  
Health, Education, and Welfare

Cris, I know that there are problems of economy and I'm glad to see that the Star has turned the corner, even if it is partly due to massage parlor ads. For at least the last two years the Post and the Star have been using the same morgue: it's not often but whenever I get to be the subject of an article, it is always accompanied by the same old picture which, with all due modesty, strikes me as less than an ideal representation of the subject. Now Cris, the other day I got a letter from Victor Cohn and he said, "Here is that picture. I'm returning it to you, but remember that the one we've replaced it with is still competing with an AP shot and thus if you have anything significant to say, you should say it only to me." So I am offering you this same opportunity, Cris, to get rid of a particular photograph that must be the only one you have in the morgue, and thus I signed this special memento, that I hope you will put behind the kitchen stove at home, "To Cris with admiration, from the son of Frankenstein."



MEDICINE, SCIENCE, AND SOCIETY 1/

by

Donald S. Fredrickson, M.D. 2/

When this evening was first planned, Alistair Cooke and I were to have appeared here together. Those of you familiar with the program "Upstairs, Downstairs" will realize that, since Lord Bellamy cannot be here, you're stuck with Hudson.

I join in your regret that Mr. Cooke could not make it. His writings and television appearances reveal his obvious affection for America. Yet he has remained detached enough to view, more clearly than we natives can, our tendency for introspection and a love of reform. From time to time, he has seemed to chide us gently for some of the contradictions in our self-conscious struggle for a more perfect society.

- Our striving concurrently for maximal consumption and minimal harm to the environment;
- The vacuum we leave with our abhorrence of elites, which we then seek to fill with a worship of celebrity;
- Our search for eternal youth that leaves us poorly prepared for growing old and dying.

The paradox I want to talk about tonight is our difficult struggle to retain simultaneously the fullest individual choice and the ultimate in authoritarian protection through governmental regulation.

---

1/ Delivered before the VIth International Congress on Thrombosis and Haemostasis, Philadelphia, Pennsylvania, June 26, 1977.

2/ Director, National Institutes of Health, Bethesda, Maryland

This last is particularly pertinent to three institutions with which you and I are conversant: medicine, science, and membership in society. As I need not tell you, the first of these institutions, medicine, is these days buffeted within and without by much angst for reform. The second, the sciences, which provide the base for a rational medicine, is not immune from impatience on the part of its public patrons. And, considering only the dilemmas generated by a common concern for health, participation in societal decision-making has become extraordinarily complicated in the past quarter-century.

I speak about these things from the point of view of a private citizen, as much as that of a government official. As one of the latter, I am aware of our obligation to avoid offending higher authority. Still, that obligation does not leave one powerless as I shall illustrate with a story appropriate to our being in this Quaker city.

There was a Quaker farmer in this state whose cow lost no occasion to abuse his gentility. Finally, one evening, as the cow overturned the full pail of milk for the second time, the farmer looked straight into its brown eyes and said: Thou dost know that I cannot kick thee. Thou dost know that I cannot curse thee. But dost thou know that I can sell thee to a Presbyterian!

Most of the major disaffections about health matters are not peculiarly American:

- The endless struggle with cost containment.
- The desire for prevention while we can achieve only palliation.

- The organizational resistance to simple solutions.

Let us rather concentrate on other matters of intense public debate in this land. The heat, if not the light, of these debates reaches across oceans. The resultants of actions and reactions to come from them have a tendency to affect our professions wherever we practice them.

The issues concern many elements with which you are familiar. Three of them are information, knowledge, and wisdom.

Like the ant or the grasshopper, man depends upon an endless stream of information. The data pour in to tell him where he is and other bits of intelligence on which to build adaptation and survival. Man is restless. Perhaps because data alone cannot tell him who or what he is--these are matters for philosophy--he constructs ever more sensors of increasing range and sensitivity. The data pile up and further processing is required. Information must be re-synthesized and ordered into knowledge. Man has traded away the fullest power of smell and certain other senses to make way in his brain for a greater capacity to store, collate, and carry out this re-synthesis.

Man also has superior powers to carry out the next higher order of mental and social activity, learning how to use knowledge well. This is wisdom. It is the highest gift, rarely achieved by any man alone--it requires the sharing of experience and the blending of values given different weight by different persons. It is a process of consensus which civilizations guard carefully and seek constantly to refine.

In the domain of health, the acquiring of the crucial knowledge of life processes has become the principal duty of professionals in the biomedical sciences. How this technical knowledge should be used was once largely the province of the professional healers. As the knowledge has increased, however, the rest of society has likewise increased its insistence upon a broader participation in the conversion of knowledge to wisdom concerning health.

It is wasteful to lament the loss of professional privilege to a more political process. It is instructive to examine the results. One is to expose the alloy of knowledge and empiricism from which so much of medicine is still constructed. It demonstrates how each increment of knowledge requires yet more to provide needed wisdom. It reinforces the requirement that all who participate in the consensus be provided with a clear view of the issue and the determinants of the decision. Finally, it highlights the unavoidable discomfort of the citizens, or those to whom they give their proxies, as the time approaches for the vote to be cast.

Let us look at three practical examples that are now much in the news.

One is saccharin, the only commercial sweetener available in America as a sugar substitute. Last March, a scientific study in Canada "proved" that commercial saccharin produced bladder cancer in rats. The Food and Drug Administration, acting under present law--societal instructions that afford it no discretion in the matter--announced its intention to ban foods containing saccharin in the United States. An exceedingly heavy



correspondence then informed the FDA, the Administration, and the Congress of a strong sentiment against this decision. Hearings were held in the Congress, bills were introduced into both Houses to prevent the FDA from carrying out its ban, and the House of Representatives this week passed such a measure as a rider on an appropriations bill. More Congressional hearings are scheduled next week. The evolution of final wisdom on this matter will take far longer. And to no one should be assigned blame for the delay.

A part of the problem is the thinness of the knowledge base. The Congress and we, the people, do not care if saccharin causes cancer in rats. Does it cause cancer in man? There are inarguable moral reasons why this hypothesis cannot be directly tested by human experimentation. To answer the question indirectly, by epidemiological studies, is a long, costly, and uncertain process. As saccharin is a weak carcinogen, we may never be able to prove what proportion of cancer of the bladder in man is due to saccharin.

Part of the problem is the inflexible base of the applicable law. In this case the Delaney Clause\* in the Federal Food, Drug, and Cosmetic Act (1938) reads "that no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal . . ."

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\*PL 85-929, as amended by PL 87-781

Should Delaney be modified to allow weighing the benefits against the risks? Shall some carcinogens be permitted in food, to cause cancer in a few, if many can be beneficiaries? How many against how few? Do we opt for continued absolutism, at least in matters of cancer, or do we permit the exercise of discretion in coping with issues that refuse to remain pure black and white? Now that new methods permit potential carcinogens to be detected in parts per trillion--a few molecules of polyvinyls from plastic containers--is absolutism compatible with the technical virtuosity that marks our civilization?

Scientific inquiry will steadily improve the base upon which such decisions must be made. The technology of mutagenesis testing--a speedy adjunct to the ponderous testing of carcinogens in animals--is burgeoning and will someday be spectacularly better. Yet its greater sensitivity will force a realization of the limits to absolute answers. Need for more exercises in developing wisdom will continue to grow.

As the Congress is perfectly well aware, the critical element in its saccharin decision is the precedent of weakening absolute authority by specific exemptions. In this, saccharin shares some similarities with Laetrile or amygdalin, the controversial cancer "cure."

A different sort of problem is presented in the current debate over Laetrile. There is no scientific evidence that Laetrile cures cancer, as has been claimed. There is also no scientific evidence that it does any biological harm as it is being used in this disease. The question of what to do about Laetrile is basically not a knowledge problem but a political problem.

Should a product or procedure be legally prohibited just because it does no good? The medical argument for doing so is that by relying on Laetrile a patient may unwittingly deny himself the benefits of accepted medical treatment. (Cynics, of course, say that the physician's loss of a patient is the real concern.) In its Federal laws, society has aligned itself with the prevailing medical opinion. The law requires that drugs be approved when they are shown to be both safe and efficacious.

The principle that the government, in its parental role (the legal principle of parens patriae), has an obligation to protect citizens from unwitting harm by monitoring the safety of pharmaceutical preparations has been accepted since the early 1900s. This protective role was later extended to include efficacy when vaccines came into common use--to avert the public health consequences of relying on an ineffective vaccine. The efficacy requirement was extended to drugs in new FDA legislation in the early 1960s.

This extension of the protective role of government is now being challenged on the ground that it is an infringement of personal freedom. Essentially, it is being argued that the government has adequately guarded the public welfare if it acts to prevent false advertising claims. The moral justification is questioned for denying a patient, whose disease is beyond the reach of accepted medical practice, access to an innocuous nostrum in which he has faith unsupported by scientific evidence. If Laetrile were part of the ritual of a religious group, would its use be protected under the First Amendment? It seems likely that it would since

there is no scientific evidence that its use is less efficacious than prayer.

Ten--by now perhaps eleven--State legislatures have acted to sustain the individual's right to self-determination in the use of Laetrile. These controversial political actions are not a blow to the integrity of science, although they are responses to a certain insufficiency of scientific knowledge. They are also not a fatal blow to the profession of medicine, although they force recognition of the principle of uncertainty that underlies the practice of medicine.

They are, I think, a severe test of the contemporary limits of the doctrine of parens patriae in matters of health. Protective authority and perfect discretion. We cannot have it both ways. Some compromise, some new wisdom will have to be forged.

A third example of friction between science and society resulting from lack of knowledge is the current debate over proposed restrictions on the use of recombinant DNA techniques. It differs from the saccharin and Laetrile examples--which concern the welfare of the individual--by being focused on concern for the welfare of the community. There is a fear--which, in our present state of knowledge, cannot be wholly allayed--that tinkering with genetic determinants may create a new environmental danger.

Pardoxically, genetic research inspires fear because so little is known about what the results may be, and it is scientifically important for exactly the same reason. All of the risks and most of the benefits are, at this stage, entirely speculative. Many scientists believe that the



techniques in question will prove as revolutionary in biology--and ultimately in the practice of medicine, as the demonstration, just a century ago (by Pasteur in 1878), that bacteria cause disease. Some others, including some scientists, see recombinant DNA research as the equivalent of atomic fission with similar potential for good and for holocaust.

Governmental responsibility for protecting the community--as distinct from protecting the individual--is an indispensable part of its obligation to promote the general welfare which is enshrined in the Preamble to the Constitution. Public health laws have an ancient legal lineage and have long enjoyed public support even when they infringe personal freedom--as in the quarantine laws and the segregation of lepers and TB patients.

There is imminent danger that laws to protect the community from the speculative hazards of using recombinant techniques will so restrict such research that it will fail to achieve results that might significantly promote the general welfare. The debate on pending legislation continues. A conscientious effort is being made by some Members of Congress to work out reasonable regulatory provisions that will harness but not hobble. Much that is crucial to the interests of the public in the processes of acquiring knowledge, and ultimately wisdom, is still in doubt.

The three examples I have mentioned represent different aspects of the government's role in the preservation of health: .

- protecting the individual from products that are unsafe;
- protecting the individual from products that are ineffective; and
- protecting the community from threats to the public health.

They involve different degrees of governmental responsibility and different levels of public acceptance of governmental intervention. They are, however, parts of philosophical problems raised by the impact of science on society. In each case, the decisions are compounded by the lack of adequate scientific knowledge. Though the resulting debate is often perceived as an attack on science, it is, in fact, a challenge to science to maximize the effectiveness of its research. If the legitimate questions being asked by the public and the legislators could be definitively answered, the problems would be dissolved or rational solutions would become obvious.

A common denominator of apparent conflicts between science and society; between science and government; and now, between society and government is, then, too often the lack of adequate knowledge. Anyone familiar with the last 25 years of biomedical science will know that generous public support has vastly increased knowledge and significantly improved wisdom. It is indispensable that such support continue. Whether the gathering of truth can be hastened or made more efficient by legislation other than appropriations is open to question.

I do believe strongly, however, that scientific inquiry and its application to medicine and health requires a new initiative on the part of its participants. It is a responsibility which must arise from within and cannot be imposed by regulation.

The lag between knowledge and wisdom is growing. The traditional ways of up-dating the state of the art are too slow. The belief that consensus

can lie only between hard covers of the standard texts is archaic. The belief that any medical matter must be beyond comprehension by the intelligent and well-informed layman is intolerable, and the preparation of technical information for lay participation in decisions is now one of the inescapable duties of the scientific community.

New efforts to meet these responsibilities are essential if public confidence in the virtues and benefits of science is to be maintained. Without that confidence, support for research from public funds will not be sustained. Even more importantly, public confidence is the only security for allowing scientists the discretion to practice their craft in a manner that will best safeguard the long-term public interest.

The cry that there is already too much science in medicine is nonsense. There is still too little. There is much in Ivan Illich's fulminations against the current practice of medicine in his Medical Nemesis that deserves careful consideration by our profession. As David Horrobin mentions in his antidotal publication, entitled Medical Hubris, one pernicious fallacy is the belief that the introduction of scientific knowledge into the doctor-patient relationship requires compassion and humanness to leave. Wisdom, too, must then depart and where are we left?

Action on the specific problems I have mentioned here tonight will undoubtedly set new precedents in the exercise of political authority over medical practice, over the scientific process, and over the ways in which wisdom is derived from data and principles.

America was born in a period of civilization called the Age of Enlightenment. Charles Morazé began his book, The Triumph of the Middle Classes, with a characterization of that Age. It was, he says, the time of "spirit." And by "spirit" he meant the definition laid out for it by Voltaire in his Dictionnaire Philosophique. "Spirit" to Voltaire was "ingenious reason."

In Western Europe, this spirit underlay not only science--but the notions of equality, tolerance, and intellectual freedom, and the creation of political structure that might encourage their growth. The American democracy, by primogeniture, became the principal heir. We naturally tend to view our history as an unbroken progression from the Age of Enlightenment.

But will future historians attach so felicitous a phrase to our present period? Are we now in only a needed cycle of reform and re-evaluation? Or are we reacting in excess; and have we passed to an Age of Disenchantment?

There is a serious need for us all, the scientist-citizens and the citizen-scientists, to identify the true from the false from among all the apparent social imperatives of our time. Swapping "ingenious reason" for apprehension and disappointment is not to gain wisdom. And not to gain steadily in wisdom is to lessen the chance for survival.



Dr. Donald S. Fredrickson  
NIH 9th Annual Honor Award  
Ceremony--Jack Masur Aud.  
June 27, 1977

Good afternoon, Ladies and Gentlemen. Welcome to the National Institutes of Health's Ninth Honor Awards Ceremony. I am happy to see how many of you have elected to join in our family celebration.

Over the years, I have been privileged to attend numerous events of this nature, many of them outside NIH. Most of these have been marked by a kind of togetherness; few of them have demonstrated to me anything like the sense of community I invariably experience here. This is why I choose to call this a "family celebration."

Those to be honored in today's ceremony include 37 Civil Service employees and 26 Public Health Service Commissioned Officers. We will salute four employees with NIH Length-of-Service Awards for having given 40 years of their lives to substantial service in the Federal government. We will also present the NIH-EEO Achievement Award of the Year, and for the first time dedicate a new Award in this area.

Today's ceremony is really one more installment in a continued story of achievement by our colleagues in 1977. In April, HEW Secretary Califano presented HEW's highest awards to six NIH staff members at the Department's Honor Awards Ceremony. At the time, the Secretary paid tribute to two other NIH representatives who had received major non-DHEW awards: (1) our latest Nobel Laureate, Dr. D. Carleton Gajdusek, and (2) Mr. James A Hickey for outstanding achievement in improving financial management in our government.

- 2 -

Today marks the first presentation of our newly established Harvey J. Bullock, Jr., Award. It was created to honor the late Mr. Bullock, known as an aggressive force in both local and national civil rights movements for well over 20 years, and a prime mover in the NIH Equal Employment Opportunity Program from its very beginning.

Belief in Institution and faith and gratitude in the people who give it its reality and purpose.

On behalf of the entire NIH family, I congratulate each of the honored guests this afternoon for the superior performances which we recognize. On behalf of those who are being honored, I thank all of their co-workers whose assistance and cooperation have helped single them out as symbols of our overall excellence.

Thank you.

# # #

**BANNING OF THE DRUG LAETRILE FROM  
INTERSTATE COMMERCE BY FDA**

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**HEARING**  
BEFORE THE  
SUBCOMMITTEE ON  
HEALTH AND SCIENTIFIC RESEARCH  
OF THE  
COMMITTEE ON HUMAN RESOURCES  
UNITED STATES SENATE  
NINETY-FIFTH CONGRESS  
FIRST SESSION  
ON  
EVALUATION OF INFORMATION WHICH THE FDA BASED ITS  
DECISION TO BAN THE DRUG LAETRILE FROM INTERSTATE  
COMMERCE

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JULY 12, 1977



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WASHINGTON : 1977

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(II)



# CONTENTS

## CHRONOLOGICAL LIST OF WITNESSES

TUESDAY, JULY 12, 1977

Kennedy, Donald, M.D., Commissioner, Food and Drug Administration, accompanied by Donald Frederickson, M.D., Director, National Institutes of Health; Guy Newell, M.D., Director, National Cancer Institute; Lewis Thomas, M.D., director, Memorial Sloan-Kettering Cancer Center; and Joseph Ross, M.D., professor of medicine, UCLA-----	Page 2
Hoffman, Herbert B., assistant U.S. attorney, San Diego, Calif.; John Keeney, Deputy Assistant Attorney General, Department of Justice; Louis Castro, deputy attorney general, State of California; Joseph Cosentino, chief medical director, board of medical examiners, State of California; and Carol Hehmeyer, assistant district attorney, San Francisco, Calif., a panel-----	189
Richardson, John A., M.D., Albany, Calif.; Robert Bradford president, Committee for Freedom of Choice in Cancer Therapy, Los Altos, Calif.; Ernst T. Krebs, Jr., San Francisco, Calif.; and Bruce Halstead, M.D., Loma Linda, Calif., a panel-----	242

## STATEMENTS

American Cancer Society, Robert C. Eyerly, M.D., prepared statement-----	370
American Medical Association, prepared statement-----	328
Board of Medical Quality Assurance, Department of Consumer Affairs, State of California, Joseph P. Cosentino, M.D., chief medical consultant, prepared statement-----	231
Burk, Dean, president, Dean Burk Foundation, Inc., prepared statement-----	385
Committee for Freedom of Choice in Cancer Therapy, Inc., Robert W. Bradford, president, prepared statement-----	280
Ermer, Walter, D.D., executive director, International Health Council, Cleveland, Ohio, prepared statement-----	375
Hoffman, Herbert B., assistant U.S. attorney, San Diego, Calif.; John Keeney, Deputy Assistant Attorney General, Department of Justice; Louis Castro, deputy attorney general, State of California; Joseph Cosentino, chief medical director, board of medical examiners, State of California; and Carol Hehmeyer, assistant district attorney, San Francisco, Calif., a panel-----	189
Prepared statement-----	231
International Health Council, Cleveland, Ohio, Walter Ermer, D.D., executive director, prepared statement-----	378
Kennedy, Donald, M.D., Commissioner, Food and Drug Administration, accompanied by Donald Fredrickson, M.D., Director, National Institutes of Health; Guy Newell, M.D., Director, National Cancer Institute; Lewis Thomas, M.D., director, Memorial Sloan-Kettering Cancer Center; and Joseph Ross, M.D., professor of medicine, UCLA-----	2
Prepared statement-----	26
Memorial Sloan-Kettering Cancer Center, Lewis Thomas, M.D., president, prepared statement-----	56
National Cancer Institute, Guy R. Newell, M.D., Acting Director, prepared statement-----	46
National Council on Drugs, John A. Owen, Jr., M.D., prepared statement-----	334
National Institutes of Health, Donald S. Fredrickson, M.D., Director, prepared statement-----	40 ✓

## ADDITIONAL INFORMATION

Richardson, John A., M.D., Albany, Calif.; Robert Bradford president, Committee for Freedom of Choice in Cancer Therapy, Los Altos, Calif.; Ernst T. Krebs, Jr., San Francisco, Calif.; and Bruce Halstead, M.D., Loma Linda, Calif., a panel-----	Page 242
Prepared statement-----	275
UCLA School of Medicine, Joseph F. Ross, M.D., professor of medicine, prepared statement (with attachments)-----	62
Articles, publications, etc.:	
Adverse Effects of Laetrile Therapy in Patients with Cancer Who Were Observed at the UCLA Hospital-----	141
An Objective Refutation of David M. Greenberg, Ph.D. and his article entitled, "The Vitamin Fraud in Cancer Quackery" by John A. Richardson, M.D., from the Western Medical Journal, April 1975-----	312



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20014

STATEMENT BY

DONALD S. FREDRICKSON, M.D.

DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ON

LAETRILE

BEFORE THE

SUBCOMMITTEE ON HEALTH SCIENTIFIC RESEARCH

COMMITTEE ON HUMAN RESOURCES

JULY 12, 1977

Mr. Chairman and Members of the Committee:

The problem of Laetrile, which we are discussing today, has several important dimensions. In the public policy area the principle that drugs must be efficacious as well as safe in order to be approved by the Food and Drug Administration is at stake. The issue simply put is: are useless nostrums to be substituted for treatments shown to be safe and useful by scientific methods? We are discussing today, therefore, a problem far greater than cancer or any other disease.

I am aware, Mr. Chairman, of the limits of the scientific method. It often cannot provide the comfort sought by those beyond the help of its restricted power. I sympathize with the frustration and grief which have led so many cancer patients and their families to try Laetrile and do not ignore the emotional dimension of this problem.

It is my purpose, however, to discuss certain of the ethical and moral problems surrounding the application of the scientific method to the clinical testing of drugs for efficacy against cancer—another important dimension of the Laetrile problem. Specifically, I would like to limit my remarks to the moral and ethical issues that have arisen from the National Cancer Institute's decision to consider conducting a clinical trial of Laetrile—a trial that by definition would involve human beings. My statement will be relatively brief. Dr. Guy Newell, Acting Director of the National Cancer Institute, will provide details, which expand upon my summary.

The present Food and Drug law requires that drugs be proved safe and effective before they can be marketed. This proof of safety and effectiveness must be demonstrated by precise and thorough testing. The precedent which underlies the implementation of this law has been that a drug shall not be tested in man without a reasonable scientific basis for assuming that it might be efficacious in man. Usually, this has meant that it has been necessary to develop proof that the drug had anti-tumor activity in animals.

As you know, Laetrile, in one or another formulation, has been known for more than 25 years. Over this extended period of time, no scientifically acceptable evidence has been presented of Laetrile's effectiveness against cancer, in either animals or man, for either prevention or cure. In his statement, Dr. Newell will amplify this point.

Let me now discuss what I consider to be the critical issue from the perspective of the scientific community: the possibility that a clinical trial of Laetrile be mounted by the National Cancer Institute. This is a critical issue because, based on past experiences, there is no valid scientific reason to put Laetrile into a clinical trial. Faced with this, the first question is: should public demand or legislation by individual states force us to break a precedent which, we believe, has served society and the public well? It is estimated that more than 50,000 individuals in this country are receiving Laetrile, some undoubtedly in lieu of other treatment known to be beneficial or curative.



Do mere numbers of people, unaccompanied by a shred of necessary scientific proof that they have been, or can be, helped by Laetrile, override those precedents that have served so well? What would be overridden is the reasonable basis that has been constructed to protect those patients who would be recruited to a clinical trial. Central to this reasonable basis is the good faith on the part of the physician and the patient both that the drug or technique to be studied has a ~~chance~~ <sup>some chance</sup> of helping the patient.

Simply stated, clinical trials have been based on the principle that drugs are tried in patients only when there is scientific evidence to believe they might help those patients. Have we ever the right to deprive a patient of a potentially useful drug, and provide instead a compound for which there is no reasonable probability of usefulness.

In any clinical trial of Laetrile, two key conditions must be met, I believe. First, no patient can be deprived of any proven therapy that might help that patient. Any individual entered into such a trial must be clearly beyond any beneficial therapy known to be effective against cancer, including surgery, radiotherapy, and chemotherapy. The second condition to be met is the principle of informed consent. Each patient must have a meticulous explanation of what is known and not known about the compounds being tested, and must have full understanding of the choices available to him when consent is given.

Trials of anticancer drugs in man present trying ethical dilemmas at best, and Laetrile, backed as it is by no scientific evidence of efficacy, compounds these dilemmas. In considering what should be its next step,

the National Cancer Institute has discussed several possible courses of action.

One option is to do no clinical trial of Laetrile, and thereby maintain that important precedent we have been discussing. The dimensions of the Laetrile problem are such that this is not a comfortable position for us.

A second option is to defer a decision on a clinical trial, and for the NCI to offer its services, in collaboration with the Food and Drug Administration, in the collection and review of clinical evidence of a kind necessary to support the effectiveness of Laetrile as an anti-cancer agent. If the use of Laetrile continues in a number of states, it is at least possible that evidence meeting scientific standards could be developed by responsible physicians who are prescribing Laetrile for certain of their cancer patients. This will be a very difficult course of action, but we need not consider it impossible.

The third option is that NCI begin a clinical trial without undue delay. In preparation for such a trial, it must thoroughly discuss and lay out those ethical issues alluded to above, as well as the considerable technical problems that would attend such a trial. The probability of a clinical trial of Laetrile providing an unequivocal result seems to be small. The possibility is considerable that even an unequivocal negative result would still not convince some proponents of this substance.

- 5 -

We will very shortly come to a decision about which of these options to adopt. Mr. Chairman, that completes my statement. You may wish to proceed to Dr. Newell's statement now, or if you prefer, I would be happy to answer questions.

# NUTRITION-RELATED OVERSIGHT REVIEW

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HEARINGS  
BEFORE THE  
SUBCOMMITTEE ON  
DOMESTIC AND INTERNATIONAL SCIENTIFIC  
PLANNING, ANALYSIS AND COOPERATION  
OF THE  
COMMITTEE ON  
SCIENCE AND TECHNOLOGY  
U.S. HOUSE OF REPRESENTATIVES  
NINETY-FIFTH CONGRESS  
FIRST SESSION

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JULY 26, 27, 28; AUGUST 2, 3, 4, 1977

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[No. 22]

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(II)

# CONTENTS

## WITNESSES

	Page
July 26, 1977:	
Opening statement of Congressman James H. Scheuer.....	1
Dr. Arnold Schaefer, Director, Swanson Center for Nutrition.....	3
John S. MacGregor, predoctoral fellow at Roche Institute of Molecular Biology.....	42
Jodie Levin-Epstein, project director, Child Care Food program and Summer Feeding program advocacy staff, Children's Foundation, Washington, D.C.....	53
Dr. Gordon Harper, pediatrician, Children's Hospital, Boston, Mass....	63
Dr. Rose Ann Langham, administrator of Nutrition Services, Office of Health Services and Environmental Quality, New Orleans, La....	77
July 27, 1977:	
Dr. Robert Rizek, chairman, USDA Nationwide Food Consumption Survey, Consumer and Food Economics Institute, Department of Agriculture, Hyattsville, Md.....	96
Arthur J. McDowell, Director, Health and Nutrition Examination Survey, Department of Health Examination Statistics, HEW, Rockville, Md.....	100
Dr. Michael Lane, Director, Bureau of Smallpox Eradication, Center for Disease Control, HEW, Atlanta, Ga.....	153
Dr. James Carter, chairman, Department of Nutrition, Tulane University, New Orleans, La.....	158
Ms. Peggy S. Kidd, Bureau for Health Services, Frankfort, Ky.....	169
Dr. Stephen Barnett, director, Migrant Health program, School of Medicine, University of Colorado, Boulder, Colo.....	178
July 28, 1977:	
Dr. Dale Hathaway, Assistant Secretary for International Affairs and Commodity Programs, Department of Agriculture.....	200
Dr. Carlos Herman Daza, Regional Adviser on Nutrition, Division of Family Health, Pan-American Health Organization.....	211
Dr. Martin Forman, Director, Office of Nutrition, Agency for International Development, Department of State.....	216
Dr. Sheldon Margen, Department of Nutritional Sciences, University of California, Berkeley, Calif.....	270
Dr. Abraham Horwitz, former director, Pan-American Health Organization.....	278
Dr. Barbara Underwood, chairman, Biological Health Department, Pennsylvania State University.....	356
Dr. Jean-Pierre Habicht, National Center for Health Statistics, Department of Health Examination Statistics, DHEW, Rockville, Md.....	362
August 2, 1977:	
Opening statement of Congressman James H. Scheuer.....	389
Dr. Gilbert S. Omenn, Assistant Director for Human Resources, Office of Science and Technology Policy.....	391
Dr. James M. Iacono, Deputy Assistant Administrator, Marketing, Nutrition and Engineering Sciences, Agricultural Research Service, U.S. Department of Agriculture.....	420
Dr. Joyce Lashof, Deputy Assistant Secretary for Health, Department of Health, Education, and Welfare; accompanied by Dr. John E. Vanderveen, Acting Director, Division of Nutrition, Food and Drug Administration.....	432

## IV

	Page
Donald Fredrickson, Director, National Institutes of Health, Department of Health, Education, and Welfare.....	444 ✓
Dr. Howard Schneider, director, U.N.C. Institute of Nutrition, University of North Carolina at Chapel Hill, N.C.....	453
Dr. William Darby, director, Nutrition Foundation, New York, N.Y.....	479
Dr. Michael Jacobson, executive director, Center for Science in the Public Interest, Washington, D.C.....	543
August 3, 1977:	
Esther Peterson, Special Assistant for Consumer Affairs, The White House, Washington, D.C.....	566
Dr. James Levinson, former director, Office of Nutrition, Agency for International Development, Washington, D.C.....	578
Sol Chafkin, director, Social Development Division, The Ford Foundation, New York City.....	581
Dr. Doris Calloway, chairman, Department of Nutritional Sciences, University of California, Berkeley.....	585
Dr. David Coursin, private consultant, chairman of Mainutrition Panel of United States-Japan Cooperative Medical Science program.....	591
Dr. Max Milner, associate director of International Nutrition Policy and Planning program, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, Mass.....	599
August 4, 1977:	
Dr. James Nielson, Deputy Assistant Secretary for Conservation Research and Education, U.S. Department of Agriculture; accompanied by Dr. Robert Rizek, Chairman, Consumer and Food Economics Institute of Agricultural Research Service, U.S. Department of Agriculture.....	622
Dr. Wilbur Cohen, dean, School of Education, University of Michigan (former Secretary of Health, Education, and Welfare).....	654
Dr. Richard Remington, dean, School of Public Health, University of Michigan, Ann Arbor, Mich.....	667
Ms. Anita Yanoichik-Owen, School of Public Health, University of Michigan, Ann Arbor, Mich.....	672
Dr. Gilbert A. Leveille, chairman, Department of Food Science and Human Nutrition, Michigan State University, East Lansing, Mich.....	675
Dr. George Owen, School of Public Health, University of Michigan, Ann Arbor, Mich.....	680
Dr. Stanley Garn, School of Public Health, University of Michigan, Ann Arbor, Mich.....	682

## APPENDIX

## ADDITIONAL SUBMISSIONS FOR THE RECORD

The Search for Hunger in America.....	689
Follow-up questions on nutrition surveillance.....	691
Response to question on Nutrition Surveillance and Monitoring in the United States.....	692
Follow-up questions and answers pertaining to human nutrition research.....	720
Letter from Vegetarian Information Service, Dr. Alex Hershaft.....	721
Letter from Dr. Robert Livingston, University of California, San Diego.....	722
National Academy of Science, Study Team 9 report on "Nutrition" in <i>World Food and Nutrition Study</i> .....	724



STATEMENT OF DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, WASHINGTON, D.C.

Dr. FREDRICKSON. I will be extremely brief, Mr. Pursell. I would like to make just several points.

First, I suppose most important is the fact that in fiscal years 1977, the NIH will spend somewhat more than \$80 million on nutrition research, and that is the largest single component of the Federal contribution toward research in nutrition.

It deals with the matter of nutrition and its effects on reproduction and conception, on the maintenance of health through infancy and adulthood, and on the aged population.

We are as much concerned with nutrition as it bears upon preserving health as we are in terms of combating or treating diseases.

Nutrition research in the United States could probably be looked at as going through three phases. The first began around 1900 or 1880 and ended about 1940. During that time, I think we saw the apogee of discovery of vitamins and certain basic nutritional requirements.

Then, following that time, we entered a second phase, in which much of the nutrition research really went underground; that is to say, it went into expanding areas of biochemistry and physiology. There was an intense desire and, I think, considerable success in reducing nutrition into its molecular terms.

I think we are now in the third phase. I am not sure exactly when we entered it, but I am quite certain we have entered a new stage in which there is an essential requirement to resynthesize a tremendous amount of that molecular information—which had been gained in the second stage—into practical ways to advise people on how to eat, to avoid diseases, and to live as long and as healthy a life as they can.

I think an important aspect of that third stage has been the ability to distinguish differences in individuals with respect to their requirements—a difference which makes the definitional problem Mr. Walker raised very, very important indeed.

At first we recognized certain unusual genetic conditions in which people who have a double dose of a gene for a disease would have a radically different dietary component.

Now we are expanding that capacity to look at people who have only one of the genes, and these, of course, represent a far greater number of people. We are beginning to divide the population into those for whom one man's meat may be another's poison. I think we are showing an intense degree of application of that kind of knowledge.

Not content, however, with the adaptation of that second phase of molecular information into practical use for man—a sort of Keynesian approach to nutrition, as I like to think about it; that is, from the cradle to the grave—NIH, in the last few years, and particularly in the last, has been reexamining its nutrition research priorities and activities.

We have a coordination committee which has finished a sort of plan and we have, as a part of that, decided to establish a new program in clinical nutrition research, which we may actually increase to the level of not an institute, but a center within one of the institutes.



We are basing that program—one of resynthesizing this information—in the two institutes that deal with human development across the whole time dimension, and that is the National Institute of Child Health and Human Development and the National Institute on Aging.

In addition to that, of course, we have a lot of activity within various institutes on specific diseases. Here, at the turning research information into use.

Here, from the National Heart and Lung Institute is just one example: a set of diet books for people with a particular genetic problem leading to high blood fats. This is a great success. Six million of these booklets have been sent out to physicians only upon their request, and we have a great many other examples of educational materials, particularly for professionals, but some of it for general populations. I think we need more of such activities.

I won't go through what all the individual institutes are doing in relationship to research on nutrition and specific diseases.

I would like to touch on the matter of coordination. We have a lot of coordination among the institutes, and we have a great deal of it between ourselves, other agencies in the department, and other departments.

Just a moment ago, Dr. Iacono described one example which I would like to amplify. For the last 2 years, the National Heart, Lung and Blood Institute has been providing \$300,000 to \$500,000 a year to support half of the cost of the USDA nutritional composition lab at Beltsville, an effort we felt very important because we wanted to increase and accelerate the information about the composition of foods.

One very practical way to use that has been to develop a computerized program—now at the University of Minnesota—where one can take a day's intake, expressed in terms of dietary foods, and get the whole nutritional composition of that intake with respect to a number of important components out in a very short time.

This is a program which is being expanded. It will tremendously increase the capability for doing diet surveys of the kind that have been expressed by the committee. So there is indeed a great deal of coordination and cooperation already going on.

I think, Mr. Chairman, those are the major points that I wanted to make, in addition to the prepared statement which I have submitted for the record.

[The prepared statement of Dr. Fredrickson follows:]

STATEMENT BY DONALD S. FREDRICKSON, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH ON THE NIH ROLE IN NUTRITION RESEARCH

Mr. Chairman and members of the committee, it is indeed a pleasure to appear before you today to discuss the NIH role in nutrition. The NIH conducts or supports the largest share of clinical nutrition research in the United States. Nutrition research is an area for which the agency is uniquely qualified to play a leading role because of the amalgam of biology and clinical medicine that is represented. NIH nutritional research dates back to 1887 when NIH began as a Hygienic Laboratory. It has always occupied an important place on our list of research priorities. Our current annual expenditures in this area are in excess of \$80 million, and NIH nutrition research programs range from nutrition in pregnant women and in infants to nutrition for the aging. Our research is concerned with nutrition as a means of preserving health and as a means of combatting disease.

Much of the best national and international research in nutrition has been developed in recent years and a great deal has been achieved, particularly in

areas such as gastroenterology, kidney physiology, endocrinology, genetics, molecular biology, and development biochemistry. These research areas are being expanded in order to improve our knowledge to specific problem areas: (1) normal growth and development; (2) maintenance of health; (3) prevention of disease; and (4) treatment of disease.

To provide a focus for nutrition research and to facilitate coordination, we have established the NIH Nutrition Coordinating Committee (NCC) with representation from all of the Institutes of the NIH. Because of the key role of nutrition research in both health promotion and disease prevention, and because nutrition research is an important trans-NIH issue, the NCC emanates from my office with a senior member of my staff as its chairman.

New concepts in nutrition are evolving. Factors such as stress, disease, drugs, food additives, and the relative amounts of many other nutritional components may affect optimal health.

The nutritional problems of the American population are of two kinds. The first is related to increased or excessive caloric intake, and the changes brought about by a food industry which utilizes a sophisticated and complex technology. The second kind is under-nutrition, vitamin deficiency, and nutritional anemia—a problem we share with less fortunate countries.

Until recent times, the approach to good nutrition has been to develop recommended dietary nutrient standards for everyone. More recently, emphasis has been shifted to restricting excess caloric intake in order to reduce the risk of certain diseases. This approach appears to be very beneficial, but it falls short of providing optimal nutrition guidance for the individual. We now have evidence that indicates that variations in susceptibility to nutrition-related diseases are a function of the unique interplay of nutrient needs and metabolic reactions derived from the genetic characteristics of each individual.

Thus the same disease treatments may be effective for some individuals and ineffective for others. On occasion, substances innocuous for one person may be seriously damaging to another. To protect those who are susceptible without denying helpful treatment to others will require greatly increased knowledge of the range of responses not only to food ingredients themselves, but also to other items that are ingested, such as food additives, allergens, and drugs.

Many genetic abnormalities which may be treated or corrected by increased intake of specific nutrients are already known. However, in some cases a nutrient in normal supply may turn out to be deleterious to some individuals. Situations of this kind are being discovered with increasing frequency. One of the sharpest challenges in nutrition research is the challenge to develop objective tests to determine which individuals of the population have unusual nutritional requirements, either for more than a normal intake of a specific nutrient or for limitation of intake because they have low tolerance to certain nutrients or other dietary components.

The ideal of nutrition research is to refine our knowledge to the point that we can provide the best nutrition possible for each individual. There is a need to improve our methods so that we can objectively evaluate the normal nutritional range of each human being.

One of the goals of biomedical research in nutrition should be to discover the basic information essential to improvement of the quality and safety of the American food supply. Another goal is to assess the nutritional needs of the population, thus enabling us to provide optimal nutrition for each segment of the population. Food fads and diets have had important and largely detrimental effects on the nutritional status of Americans.

Improved methods to assess nutritional status and to detect marginal deficiencies in man are under active study, along with development of reliable techniques for determining bioavailability of nutrients from foods supplements and synthetic diets taken orally or intravenously.

As I stated earlier, the NIH is stressing the resynthesis of such information and, in doing so, is highlighting clinical nutrition. Major responsibility for these programs resides in the National Institute of Child Health and Human Development and the National Institute on Aging, which support research relating to the springtime and the autumn of human life, the two periods when humans are most vulnerable. The program includes studies on the role of nutrition in fertility and reproduction; the effects of nutrients on fetal development; the special techniques for infant feeding for the low birth weight babies, as well as the relation between infant feeding and future development of taste preferences and food selection. We support important studies on the correlation between genetic and



environmental factors and obesity and bone strength; and we are examining the relationship between diet in childhood and adults life and the aging process. Particular emphasis is being directed toward the study of hormonal and gastrointestinal changes, and we are trying to understand the behavioral sequelae of various nutrient interactions in the development of "senility," or senile behavior. The clinical program strives to understand the interaction of genetic and nutritional factors, and to delineate the role of various nutrients singly and in combination to prevent disease and to maintain health throughout life from conception to old age.

Although the responsibility for nutrition research in the very young and in the aging resides in two Institutes, nutrition research as it relates to prevention and treatment of specific diseases is given important emphasis in many other Institutes. Let me mention a few examples:

The primary focus of the National Heart, Lung, and Blood Institute's nutrition program is prevention of cardiovascular disease through reduction of those risk factors which are amenable to nutritional modification or treatment. Specific research issues include the role of sodium and other minerals in the development of hypertension, the relationship of obesity to hypertension, and research into modification of dietary habits. The role of nutrition in development of arteriosclerosis is also extensively studied.

At present the National Cancer Institute is pursuing research on the role of diet in the development and prevention of cancer, as well as the role of diet and nutrition in the treatment and rehabilitation of the cancer patient.

The National Institute of Arthritis, Metabolism, and Digestive Diseases is supporting research on nutrition as it relates to obesity and diabetes and its use in the treatment of obese and diabetic patients. The role played by fiber in certain diseases and the nutritional needs of hospitalized patients are also under study.

The National Institute of Dental Research supports research concerning the role of nutrients in the prevention of caries, periodontal disease, and congenital defects of the oropharynx.

The NIH interacts with many Federal and nonfederal agencies, including the U.S. Department of Agriculture, the Food and Drug Administration, private foundations, and professional societies. In the area of nutrition education, the NIH through its Institutes cooperates with the American Academy of Pediatrics, the American Heart Association, and the American Diabetes Association. Liaison is also maintained between the NIH and the Food and Nutrition Board of the National Research Council of the National Academy of Sciences. Our coordination efforts are far from perfect, but we are struggling to improve them.

In summary, Mr. Chairman, our major responsibility in nutrition research must be to develop a knowledge base and to develop the wisdom to make clinical application of our findings for the benefit of all people of this Nation. This is where our expertise lies, and this is what the public expects. This completes my prepared statement. I shall be pleased to answer any questions you may have.

Mr. SCHETER. Very good.

We will proceed with the hearing.

Bill?

Mr. WELLS. Dr. Fredrickson, your testimony referred to HEW having the largest component of the Federal Government support of nutrition research, and this is largely devoted to a disease-oriented research.

With the previous testimony having made a very large point of the fact that preventive medicine—or the relation of nutrition to preventive medicine—is probably one of the major new areas in nutrition research, how is this going to affect your own research strategy?

Dr. FREDRICKSON. Mr. Wells, let me take fiscal year 1976, to give a very brief answer to your question. We had approximately \$63 million under nutrition research by the usual definitions.

It is interesting that in that fiscal year \$43 million of that \$63 million went for research on normal development and the prevention of disease; \$5.1 million was allocated to nutrition research related to

Remarks  
on the Occasion  
of  
National Hispanic Heritage Observance\*  
by  
Donald S. Fredrickson, M.D.\*\*

Buenos Días Amigos!

Es un placer para mi tener esta oportunidad de tomar parte, con ustedes, en celebrar "National Hispanic Heritage Observance" aquí en los Institutos Nacionales de la Salud.

La cultura Hispana llegó a nuestras costas mucho antes de la del Anglo. Esta es la base del orgullo de nuestra población Hispana en este país. Y nunca será olvidada.

The President of the United States wants to remind us of this Hispanic Heritage and has issued the following proclamation:

---

\* At the Masur Auditorium, National Institutes of Health, on September 12, 1977.

\*\* Director, National Institutes of Health, Bethesda, Maryland.



## NATIONAL HISPANIC HERITAGE WEEK, 1977

-----  
BY THE PRESIDENT OF THE UNITED STATES OF AMERICA

## A PROCLAMATION

The Hispanic heritage of over sixteen million Americans, representing a broad diversity of cultures, has enriched our Nation by contributing to the advancement of art and science and by affirming the importance of family bonds and community spirit.

Today, Americans have come to recognize the important role of the Hispanic community both in the life and work of the United States and in our efforts to achieve understanding, mutual respect and common purpose with the Spanish-speaking nations of this hemisphere.

In recognition of our Hispanic heritage, the Congress, by joint resolution approved September 17, 1968 (36 U.S.C. 169f), has requested the President to issue annually a proclamation designating the week including September 15 and 16 as National Hispanic Heritage Week.

NOW, THEREFORE, I, JIMMY CARTER, President of the United States of America, do hereby proclaim the week beginning September 11, 1977, as National Hispanic Heritage Week and call upon the people of the United States, especially the educational community, to observe it with appropriate ceremonies and activities; to reflect on the influence of Hispanic culture in our land; and to encourage the full participation of Hispanic Americans in every phase of American life.

IN WITNESS THEREOF, I have hereunto set my hand this twenty-ninth day of August, in the year of our Lord Nineteen hundred seventy-seven, and of the independence of the United States of America the two hundred and second.

JIMMY CARTER

OPENING REMARKS AT THE NIH/NCI CONSENSUS DEVELOPMENT MEETING  
ON BREAST CANCER SCREENING\*

by

Donald S. Fredrickson, M.D.\*\*

In these next three days we shall be tinkering with the processes of scientific evaluation. We will be engaged in an experiment in quickening the approach to certain decisions about scientific matters that have important social dimensions.

The traditional methods of arriving at conclusions within the scientific community involve experimentation, the preparation of a report of findings and hypotheses, careful editorial review and criticism of that report, and after what is usually considerable delay, its publication. As this contribution falls into the open literature, it diffuses into general awareness and submits to further evaluation in a number of ways. Eventually it will become grist for review and perhaps resynthesis along with prior and other contemporary knowledge. With even more time it may become doctrinal wisdom, encased between hard covers of authoritative texts.

The method sounds slow and tedious. And it is, but with good reasons. The conversion of information to knowledge, and knowledge to wisdom, cannot be accomplished instantaneously. There are limits to its acceleration, and one approaches cautiously any perturbation of the dynamics of a system, derived as it would seem almost according to some natural laws.

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\* Presented on September 14, 1977, in the Masur Auditorium, Clinical Center, National Institutes of Health, Bethesda, Maryland

\*\* Director, National Institutes of Health

Yet there are arguments for venturing to play with the traditional ways of handling information as they are working today in the biomedical sciences. The method does not seem attuned to a much increased demand for wisdom . . . and better quality wisdom, if you please, consummated with shorter delays. The technology arising from medical research is burdening society with questions of cost and effect which create many of these demands. Added to impatience for more timely assessments are other imperatives: that there be broader, more open participation and a more careful balancing of the inevitable biases in any controversy, that there be a clear record of the deliberations, and that any conclusions be explained in terms suitable to the varied audiences which will have an interest in the outcome.

Needless to say there are many other requirements: to recognize, and cope with, the rapidity with which knowledge--and consensus--become obsolete; to select those questions that are susceptible of solution; to welcome consensus on what we do not know as being no less useful than new revelations of truth; and to confine our authority to the limits of our expertise.

It is this latter concern that has led us to call these exercises a search for technical consensus. We believe that the scientific community must avoid all pretension of ultimate wisdom in its seeking of consensus. If we can lay out the state-of-the-art--what it is we know and do not know--we will adequately serve those other agencies of Government and of society which will lay their own value judgments upon the base we provide them.

In these extraordinary times when the setting of standards is increasing in many spheres of medicine and health practices, I stress this latter point emphatically. NIH--and the great biomedical community of which it is a center--will meet its responsibilities if it sticks to data scientifically derived. Catalysis of some modest increase in the rate of resolution of differences of opinion on technical issues is a goal sufficiently ambitious for one Agency, and for one community of interests.

As a final gesture to ward off self-deception, I would hasten to admit that the startling, new method we are unveiling today is little more than open, frank discussion of the available facts. By using it wisely, we may find that we can roll a little faster toward temporary resolution of questions to which many people anxiously need an answer. If we do this, people will be gentle with us for appearing to think we have re-discovered the wheel.

Speaking for the whole community, I am most grateful to all of you who have agreed to participate as panelists, and to all others who come as public participants or observers to this exercise.

In closing this opening, I would offer an historical reflection. An exuberant belief in the perfectability of society, through continuous improvement in science, was the hallmark of the 18th century Age of Enlightenment. Nowhere was hubris greater than in France and none more enthusiastic than men like Voltaire, Condorcet, and Saint-Simon. In the 19th century this belief in scientific salvation and inevitable progression



of civilization tended to return to the ancient assumption that history is cyclical and human institutions impervious to lasting improvement. There are ample adherents to this persuasion in this 20th century, many of them despairing critics of all new technologies.

In a setting such as this place today, where medical practices are upheld and refined by the achievements of a skeptical but positivist science, such pessimism is poorly tolerated.

I hope you, too, share that essential optimism--and that you will have retained it when this exercise has closed.

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## EDITORIAL

### Seeking Technical Consensus on Medical Interventions

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The evolution of science has yielded a time-tested process for the conversion of information to knowledge, and knowledge to wisdom. Involved are familiar and accepted phases: posing the question, conducting the experiment, preparing the report, receiving editorial review and criticism, and (sometimes after considerable delay) achieving publication. As the contribution passes into the literature, it diffuses into general awareness and undergoes further evaluation in a number of ways. Eventually it will become grist for resynthesis along with other knowledge. With even more time it may become doctrine encased between the covers of authoritative texts.

The method is slow and tedious, but for good reasons. There are limits to its acceleration and one approaches cautiously any perturbation of the dynamics of a system that seems almost to derive from natural law.

Yet one hears arguments today for modifying the traditional ways of handling information in the biomedical sciences. For these older ways are not particularly attuned to a rising demand for wisdom—and better-quality wisdom, if you please, served up with shorter delays—about medical questions that have important social dimensions. This demand is created by physicians, planners, payers, politicians, patients, and others who want authoritative opinions on health technologies.

There is an inescapable need to enhance the present highly informal but often haphazard process for creating authority by increments of opinion. Failure to do so can only result in further uncertainty about medical inventions that is either unnecessary or intolerable. Another consequence will be the rise of ambitious creations for “technology management,” which may rely unduly on regulatory measures or marketing controls. In this issue of *CLINICAL RESEARCH* is an article describing a novel exercise to hasten the search for consensus in the old-fashioned way.

“National Institutes of Health Consensus

Development Panel: Statement of Recommendations on Breast Cancer Screening” summarizes the activities, conclusions, and recommendations of an NIH-NCI panel convened to examine issues and the state-of-the-art in breast cancer screening, particularly through use of mammography.

Recent findings have raised serious questions about risks and benefits associated with mammography as an aid to cancer case-finding. Among interested scientists and clinicians, opinions were sharply divided. The magnitude of the issue was indicated by the fact that nearly 300,000 women were voluntary participants in a government-sponsored screening program that included the use of this technique.

Accordingly, in September 1977, a 16-member panel—carefully chosen to include knowledgeable clinicians, scientists, other experts, and interested laymen—met in open session for three days at Bethesda, Maryland. The panel reviewed available data, heard the views of expert and lay witnesses, and developed conclusions and recommendations. These represent the consensus judgment of the panelists.

The proceedings reflect several imperatives that must be met in attempts to hasten resolution of scientific issues in this way:

- The need to select questions that are susceptible of solution;
- The need for broad and open participation, and a careful balancing of inevitable biases among the presenters and deciders;
- The importance of making available a clear record of deliberations;
- The need to explain conclusions in terms suitable to the varied audiences with an interest in the outcome;
- The need to achieve consensus on the gaps in knowledge as well as on the advances; and
- The desirability of confining the search for authority within the limits of expertise assembled.

It is this last concern that has led us to speak of

a search for *technical consensus*. We believe that the scientific community must avoid all pretension of ultimate wisdom in these exercises. If we lay out the state-of-the-art—what it is we know and do not know from data scientifically derived—we will serve medicine and society through provision of a sounder base on which further value judgments can be laid.

Further programs for consensus development on controversial medical interventions are planned and will be announced in CLINICAL RESEARCH.

DONALD S. FREDRICKSON  
Director  
National Institutes of Health  
Bethesda, Maryland

## OPENING REMARKS

at

1977 NIH ASIAN-AMERICAN CULTURAL CELEBRATION\*

by

Donald S. Fredrickson, M.D.\*\*

I'm delighted to be on hand for the opening of the 1977 Asian-American Celebration at NIH and to welcome all of you here.

The celebration of various cultural weeks and days has become a happy tradition at NIH. I enjoy them personally, and I attend as many of them as I possibly can.

In these celebrations we set aside some time to recognize and pay tribute to the various ethnic and racial groups that make up the NIH community and the greater Washington community in general.

These celebrations are a reminder of our rich and varied cultural heritage. They help bring us closer together. They are instructive. They give us an invaluable insight into different life styles, different ways of looking at art and music and dance and the theater. And certainly not least, they are fun, a brief but happy respite from a busy day at our labs, our desks, and our duty stations.

The Asian and Asian-Americans have a lively and active cultural life. We at NIH are very familiar with their great contributions to biomedical science and to science in general, and their rich cultural achievements as well are no surprise to us.

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\* Presented at the National Institutes of Health, 14th Floor Auditorium, on September 15, 1977.

\*\* Director, National Institutes of Health, Bethesda, Maryland.



I am told that the Asian-American Cultural Committee's logo this year means "long-life." Certainly, Asian-Americans have done a great deal to make our own lives not only longer but richer, more interesting, and more varied. We at NIH are honored to be able to share the cultural life of our fellow Asian-American citizens.

We are also honored to have with us today Mr. Thavanh Svengsouk, who will be our first host this afternoon. Mr. Svengsouk is the senior language editor of the Laos Service of the Voice of America and serves as deputy to the chief of the Laos Service at VOA. Mr. Svengsouk will open our Asian-American Cultural celebration with the Laotian part of the program.

Mr. Svengsouk . . .

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DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20014

STATEMENT BY

DONALD S. FREDRICKSON, M.D.

DIRECTOR

NATIONAL INSTITUTES OF HEALTH

ON

BIOMEDICAL RESEARCH RELATED TO PREVENTION OF DISEASE

BEFORE

THE SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH

COMMITTEE ON HUMAN RESOURCES

UNITED STATES SENATE

September 16, 1977

Mr. Chairman and Members of the Subcommittee:

I welcome the opportunity to discuss with you those activities of the NIH particularly related to prevention of disease and disability. This should include mention of some of the difficulties associated with identifying which research endeavors will ultimately enhance our ability to prevent, detect, or ameliorate the effects of established disease.

We are all familiar with the epigram relating prevention and cure. In many instances the cost-benefit ratio is not an ounce for a pound, but a thousand-fold greater. The standard example is development of immunization measures against infectious diseases, particularly those of early childhood, and their administration to the population at large. This represents the classic union of basic and clinical research and its application through public health measures to the common good.

Prevention is a term that means many things in many contexts. It ideally rises from understanding of the causation of disease. At the least, it is derived from empirical observation of factors which appear to prevent the onset of disease or influence its course. The practice of prevention is eventually embodied in what constitutes good health care practice. In this narrow concept, prevention research falls within the realm of effort usually described as applied or targeted research; that is, the research goal is well defined even if the disease mechanism is imperfectly understood.

A sizeable portion of NIH research does not, however, relate to prevention in this narrow sense. I refer to research on basic life processes and the etiology, pathophysiology, and mechanisms of disease.

We know that many of the classic advances in prevention of communicable disease did not depend on understanding of disease processes. Yet major advances against hitherto unresolved problems--chronic and degenerative disease, genetic disorders, environmentally induced diseases, and problems related to nutrition and aging--will depend more and more upon fundamental understanding and come less and less from empiricism. Thus, any assessment of the scope and merit of prevention research must include an acknowledgment of the difficulty of drawing arbitrary distinctions.

#### Prevention Research at NIH

Recently, at the request of Subcommittee staff, we examined all NIH research activities to identify and describe those related to prevention. A report of that survey has been made available to you. We identified two principal types of prevention research, namely:

1. Primary Prevention - Research aimed at development of interventions to be employed before the biologic onset of disease. This includes research and education directed at changing behavior such that disease will be averted or ameliorated; and

2. Secondary Prevention - Research directed toward interventions after the disease can be detected but to suppress its progression to symptomatic or more serious stages.

In addition, the NIH units responding to the survey also provided a discussion of prevention in the context of their missions and programs. These papers are instructive as descriptions of the "state-of-the-art" in their respective areas and the relationships of basic research to



primary and secondary prevention. They also illustrate the difficulty of affixing apparently straightforward labels to the myriad of activities comprising the NIH research program.

Most NIH components characterized the definitions as too restrictive. If one examines the full range of research efforts in terms of predictable outcomes and applications, it seems clear that "prevention" is hard to pin down. Yet the questions asked deserve a reasonable answer as we formulate goals for the future.

I have included summary tables from this report for easy reference. Table I summarizes NIH prevention activities in programmatic terms. The range of programs is enormous. Research on the cellular and molecular basis of disease may permit the development of diagnostic procedures to predict onset of a disease. Other research begins with a focus on epidemiology, or incidence of disease. Here we find significant efforts in several institutes, including identification and modification of risk factors for heart disease, development of a less hazardous cigarette, and new approaches to identifying causes of diabetes. Other areas of particular promise are those relating to vaccine development and reduction in infant mortality through improved understanding of high risk pregnancy and fetal medicine.

You will note that Table II indicates that for fiscal year 1976, \$270 million, or 13%, of the NIH budget was devoted to prevention research defined in this restricted manner. I would like to call your attention to two features of that table which are, in my view, significant:

1. First, research expenditures of the National Institute of Environmental Health Sciences are not included in the total. The

analysis of its activities could not be made on the same basis as for other Bureaus, Institutes, and Divisions. The Institute does not support an extensive program of research on disease prevention per se, according to the rigid definition employed for this study. Yet, by other reasonable definitions, almost all of the program of this important Institute is devoted to prevention. Its task is the understanding of the effects of environmental agents that threaten human health. Its methods and information provide regulatory agencies with much of the data base required to promulgate standards and other means to protect the population.

2. Having defined the magnitude of NIH resources directed specifically at prevention research, I believe it valuable to compare it to our other efforts in proper perspective. The bulk of research on disease prevention--as defined for purposes of the report--is, in fact, applied research. Approximately one-quarter of our annual applied research budget, then, is now directed toward prevention.

In spite of the definitional problems just noted, the NIH has profited from the analysis described in the report just submitted. The estimates are necessarily "soft," but a base is established for continuous tracking of the portion of the total effort directed at prevention. This review has enabled us to be even more sensitive to the distribution of effort among initiatives in prevention, amelioration, and cure. It has helped to remind us that one measure of the success of research must be the enlargement of the first initiative and gradual shrinkage of the others.

There are practical as well as philosophical implications. In the increasing competition for the research dollar, the priority-setting must involve hard choices between opportunities for prevention on the one hand and treatment, on the other. In both instances, choices must be informed by a realistic assessment of available opportunity as well as need. These choices mean more preliminary analysis of benefit vs. cost, as well as likelihood of success.

#### Health Education

If the ultimate use for the findings of prevention research is their incorporation into good health practice, then research efforts must be complemented by activities aimed at education of those who must use the information derived from research. The NIH is engaged in extensive programs of health education directed at research investigators, health professionals, and the lay public. The primary goal of these efforts is to encourage the development of consensus regarding the application of research findings to health care. This, we view as a natural extension of the activities and interests of NIH. In health, as in other areas of importance to the daily lives of our citizens, people want and need expert opinions and advice, and much of that expertise may be found at the NIH or in the research and health communities with which the agency relates.

It should be noted, however, that we are not, and should not be, the only agency involved in health education, nor is this an effort which can be left entirely to the public sector. Our efforts are

complemented by those of other components and by a variety of private and voluntary organizations engaged in health education. The greatest portion of the NIH health education effort is directed to health professionals, rather than to the public, and, in our view, the balance is a reasonably appropriate one.

### Disease Control

In recent years, we have seen the addition of a number of legislative mandates for so-called "disease control" programs. Here, I would note that the first and most traditional Government role has been in the area of disease control, beginning with public health measures designed to control or eliminate the spread of infectious diseases. As those problems have been diminished, the concept of disease control has been broadened to include a variety of diagnostic and screening efforts for chronic and acute diseases.

From our standpoint, it is useful to make a distinction between control and demonstration activities. In our view, the primary role of NIH in this area is to contribute to knowledge development and to its dissemination within the practicing community. We do not interpret control as extending either into the regulation of health care practice or commitment to long-term provision of direct health care services. Rather, we see it as an extension of research along the continuum from basic investigation to application into the health care system. The appropriate involvement for NIH, then, is in areas where there remains a scientific question to be answered. Such questions may relate to



efficacy, feasibility of application within the health care system, or relative risks and benefits of alternative prevention or treatment measures.

We recognize, however, that there are enormous pressures for the Federal Government and other participants in the health care system to expand efforts directed toward control of disease. Many components of NIH relate effectively to other Federal agencies or private groups in this area. The more difficult problems arise in areas such as cancer research where there are no complementary Government or private agencies capable of pursuing major initiatives in demonstration and control. The pressures here are made more acute by the recent focusing of Congressional and public attention on special disease problems, such as diabetes, arthritis, and epilepsy. In all these areas, we have recently seen prestigious commissions recommending an expansion of the Federal role in research and treatment. A recurrent suggestion is that there should be established national centers combining research and outreach programs.

As you know, Mr. Chairman, we have been examining the roles and boundaries of NIH with a view toward determining what would be a manageable mission for this agency within the limits of resources and management capabilities. There are difficult problems here and we do not claim to have resolved them. There is a need for aggressive participation by the research community, the Federal sector, and private agencies concerned with health services, acting together in complementary fashion to arrive at a rational solution and expression of the appropriate role for NIH and other Federal agencies. We look forward to discussing these issues in more depth as these hearings progress.

The analysis of prevention activities of each Bureau, Institute, and Division of NIH is described in detail in the report before you, Mr. Chairman. They collectively provide illustration of some of the principles which I have touched upon. I will be glad to discuss them in more detail or to answer other questions you may have.

TABLE I  
NATIONAL INSTITUTES OF HEALTH  
RESEARCH SUPPORT FOR DISEASE PREVENTION  
FY 1976 & 1977

(Dollars in Thousands)

Organizational and Program Activity	Primary Prevention		Secondary Prevention		Total
	1976	1977	1976	1977	
National Cancer Institute					
Identification of a Less Hazardous Cigarette	\$7,740	\$6,000			
Identification of Chemicals for Carcinogenicity	10,000	11,000			
Vitamin A Derivative in Prevention of Bladder Cancer	4,300	5,000			
Virus Research	4,137	5,400			
Reduced Radiation Exposure	1,179	900			
Identification of New Cancer Causes	6,000	6,200			
Nutrition and Cancer	2,283	3,475			
Smoking Education and Information	669	634			
Occupationally-Associated Cancer	500	500			
The Tyler Texas Workers' Cancer Surveillance and Education Project	995	950			
The Louisville Vinyl Chloride Workers' Cancer Surveillance and Education Project	900	1,000			
Irradiation-Related Thyroid Cancer	11	25			
Cancer Control Communications Network Program	750	1,000			
Coordination and Support to Other Federal Agencies	4,000	8,000			
Subtotal	<u>43,464</u>	<u>50,084</u>			
Control and Detection of Cancer			20,337	23,247	
General Cancer Diagnosis			7,650	8,300	
Immunodiagnosis			3,500	3,400	
Subtotal			<u>31,487</u>	<u>34,947</u>	
Total Primary and Secondary Prevention			74,951	85,031	

Organizational and Program Activity	Primary Prevention		Secondary Prevention		Total
	1976	1977	1976	1977	
<u>National Heart, Lung, and Blood Institute</u>					
<u>Heart and Vascular Diseases:</u>					
Arteriosclerosis	41,869*	29,436*	-	-	
Congenital & Rheumatic Heart Diseases	2,200	2,400	-	-	
Coronary Heart Disease	**	**	3,020	1,440	
Sudden Cardiac Death	-	-	3,200	4,140	
Subtotal - Cardiovascular	44,069	31,836	6,220	5,580	
<u>Lung Diseases:</u>					
Respiratory Distress Syndrome	2,000	1,500	-	-	
Cystic Fibrosis, Bronchiolitis	280	1,000	-	-	
Fibrosis, Immunologic Diseases	2,000	2,100	2,000	2,100	
Respiratory Failure	380	250	750	1,000	
COLD	-	-	2,500	3,500	
Subtotal - Pulmonary	4,660	4,850	5,250	6,600	
<u>Blood Diseases and Resources:</u>					
Cooley's Anemia	750	800	1,000	1,100	
Sickle Cell Disease	2,000	2,200	3,500	3,800	
Thrombosis, Hemostasis	750	800	-	-	
Blood Resources	500	600	-	-	
Subtotal - Blood	4,000	4,400	4,500	4,900	
Totals	52,729	41,086	15,970	17,080	
			68,699	58,160	

\*Clinical Trials, such as those included under Arteriosclerosis, generally require heavier funding during the more costly, earlier phases.

\*\*Primary Prevention Research on Coronary Heart Disease is included under primary prevention of arteriosclerosis.



- 3 -

Organizational and Program Activity	Primary Prevention		Secondary Prevention		Total
	1976	1977*	1976	1977*	
<u>National Institute of Allergy and Infectious Diseases</u>					
Virus Vaccines	7,138				
Bacterial Vaccines	4,098				
Allergic Diseases	134				
Biological Regulation of Vectors	1,952				
Subtotal	<u>13,322</u>				
<u>Transplantation Immunology Allergic Diseases and Clinical Immunology Antiviral Substances</u>					
Subtotal			3,321		
			2,685		
			<u>3,502</u>		
			<u>9,508</u>		
<b>Total Primary and Secondary Prevention</b>					<b>22,830</b>
<u>National Institute of Arthritis, Metabolism and Digestive Diseases</u>					
Arthritis, Bone and Skin Diseases	531		635		
Diabetes, Endocrine and Metabolic Disease	462		2,281		
Kidney, Urologic and Blood Diseases	703		1,532		
Digestive Diseases and Nutrition	1,715		2,301		
Subtotal	<u>3,411</u>		<u>6,749</u>		
<b>Total Primary and Secondary Prevention</b>					<b>10,160</b>

\*No major change expected

Organizational and Program Activity	Primary Prevention		Secondary Prevention		Total
	1976	1977*	1976	1977*	1976
<u>National Institute of Child Health and</u>					
<u>Human Development</u>					
Contraceptive Development	6,338				
Contraceptive Evaluation	5,217				
High Risk Pregnancy and Fetal Medicine	4,805				
Fetal Pathophysiology	4,005				
Prematurity and Birth	2,312				
Sudden Infant Death Syndrome	2,421				
Clinical Nutrition	1,104				
Mental Retardation	6,886				
Subtotal	33,088				
Disorders of the Newborn			4,017		
Diagnosis and Evaluation of Mental Retardation			5,336		
Clinical Nutrition			3,440		
Learning Disorders			565		
Subtotal			13,358		
Total Primary and Secondary Prevention					46,446
<u>National Institute on Aging</u>					
Societal Research and Prevention	280	470	50	80	
Psychologic, Neurologic Research and Prevention	610	1,000	-	-	
Research to Prevent Treatment of Normal Changes	500	820	-	-	
Nutrition Research and Prevention	360	600	-	-	
Subtotal	1,750	2,890	50	80	
Total Primary and Secondary Prevention			1,800	2,970	

\*No major change expected

Organization and Program Activity	Primary Prevention		Secondary Prevention		Total
	1976	1977*	1976	1977*	1976 1977*
<u>National Institute of Dental Research</u>					
Caries	3,804		48		
Periodontal Diseases	167		37		
Restorative Materials	211		--		
Pain Control & Behavioral Studies	--		525		
Soft Tissue Stomatology & Nutrition	--		100		
Dental Research Institutes	173		150		
Intramural Research	--		258		
Subtotal	<u>4,355</u>		<u>1,118</u>		

Total Primary and Secondary Prevention 5,473

\*No major change expected

Organization and Program Activity	Primary Prevention		Secondary Prevention		Total
	1976	1977*	1976	1977*	
<u>National Institute of Environmental Health Sciences</u>					
Extramural Research Programs					
Environmental Mutagenesis and Reproductive Toxicology					
Environmental Pharmacology and Toxicology					
Etiology of Environmental Diseases and Disorders					
Environmental Pathogenesis Subtotal					
Intramural and Contract Research Programs					
Pharmacology					
Environmental Toxicology					
Environmental Mutagenesis					
Environmental Biophysics					
Biometry					
Environmental Biology and Chemistry					
Research Contracts					
Subtotal					
Total					

Total Primary and Secondary Prevention

\*No major change expected

See NIEHS Report for funding allocation.



Organization and Program Activity	Primary Prevention		Secondary Prevention		Total
	1976	1977*	1976	1977*	
National Institute of General Medical Sciences					
Cellular and Molecular Basis of Disease					
Genetics	466		328		
Pharmacology-Toxicology	--		4,637		
Clinical and Physiological Sciences	425		1,008		
Biomedical Engineering	455		3,708		
Subtotal	--		3,254		
	1,346		12,935		

Total for Primary and Secondary Prevention 14,281

National Eye Institute					
Retinal and Choroïdal Diseases	252	2,264**	4,410		
Corneal Diseases	267		1,379		
Cataract	270		11		
Glaucoma	354		800		
Sensory and Motor Disorders of Vision	73		420		
Research Management and Program Services	55		286		
Subtotal	1,271		7,306		

Total for Primary and Secondary Prevention 8,577

Clinical Center					
Blood Bank Department	189				189

\* No major changes expected  
\*\* Only major change expected

Organization and Program Activity	Primary Prevention		Secondary Prevention		Total
	1976*	1977**	1976*	1977*	
Division of Research Resources					
General Clinical Research Centers	3,540		1,740		
Animal Resources	50		50		
Biomedical Research Support Grant	23		34		
Subtotal	<u>3,613</u>		<u>1,824</u>		

Total for Primary and Secondary Prevention 5,437

\* Estimated

\*\*No major change expected

Organization and Program Activity	Primary Prevention		Secondary Prevention		Total	
	1976	1977*	1976	1977*	1976	1977*
<u>National Institute of Neurological and Communicative Disorders and Stroke</u>						
Neurological Disorders Program	1,769		1,851			
Fundamental Neurosciences Program	--		213			
Communicative Disorders Program	244		970			
Stroke and Trauma Program	1,389		2,940			
Intramural Research Program	572		627			
Subtotal	<u>3,974</u>		<u>6,601</u>			
Total for Primary and Secondary Prevention					10,575	
NIH Total for Primary and Secondary Prevention**					\$267,418	

\*No major changes expected

\*\*Excluding NIEHS

September 1, 1977

TAB II  
1976  
(Dollars in Millions)

Percent  
Prevention  
(Primary +  
Secondary)

BID	Primary Prevention	Secondary Prevention	Total Prevention	Total Budget	Percent Prevention (Primary + Secondary)
NCI	43	31	75	761	10
NHLBI	53	16	69	369	19
NIAID	13	10	23	126	18
NIAMDD	3	7	10	175	6
NICHD	33	13	46	136	34
NIA	2	0.050	2	19	9
NIDR	4	1	6	51	11
NIEHS*	-	-	-	-	-
NIGMS	1	13	14	187	8
NEI	1	7	9	50	17
NINCDS	4	7	11	140	8
CC	0.189	-	0.189		
DRR	4	2	5	130	4

NIH TOTAL 163

270

2144\*\*

13\*\*

\* See NIEHS Report

\*\* Approximate - Does not include Clinical Center and NIEHS



Remarks  
on the occasion of  
DRR 15th Anniversary Luncheon\*

by  
Donald S. Fredrickson, M.D.\*\*

It is a welcome change, in the middle of a busy day, to be invited to a party commemorating a notable event in the evolution of the National Institutes of Health. I am delighted to have this opportunity to wish the Division of Research Resources a Happy Birthday and, especially, to express to you, its staff and Advisory Council members, my earnest hopes and sincere wishes for many happy future birthdays marking your continuing fruitful contribution to the fulfillment of the NIH mission.

As last July marked the 15th anniversary of the Division's birth, it is--from a purely chronological point of view--in its mid-teens which, you will agree, if you recall your own youthful experiences or have some current sufferers in your household, is an awkward age. As fashions change, there have been many definitions of adolescence. The one that defines it as the time when kids stop collecting stamps and start playing post office is probably out-of-date but, in my house at least, it is still relevant to describe adolescence as the period in which the young suddenly feel a great responsibility for answering the telephone. You can, no doubt, think of more annoying or worrying manifestations and, like any normal adult, you will conclude that things weren't that bad when you were a teen-ager.

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\* Held at Bish Thompson's Restaurant, Bethesda, Maryland, on September 19, 1977

\*\* Director, National Institutes of Health, Bethesda, Maryland.

Do you remember the mother who lectured her small daughter, a seven or eight year-old, and said "If you keep on being so naughty, *your* children will be naughty, too" to which the bright youngster replied "Oh, Mummy, you just gave yourself away!!."

The waywardness of youth has honorable precedent. In Shakespeare's *The Winter's Tale*, a character complains:

"I would there were no age between ten and three-and-twenty, or that youth would sleep out the rest; for there is nothing in the between but getting wenches with chold, wronging the ancientry, stealing, fighting."

However, there are those who take a more kindly and sympathetic view of fifteen-year-olds. John Armstrong, the 18th century Scottish physician and poet, regarded that age as the threshold of adulthood; he wrote

"Ye Youths and Virgins, when your generous blood  
Has drunk the warmth of fifteen summers, now  
The Loves invite; now to new rapture wakes  
The finish'd Sense; . . ."

Fortunately, the analogy between human growth and institutional development does not always hold true. DRR--or DFRR, as it was then called--had "the finish'd Sense" and woke to its new rapture right from the start. You have 15 years of solid accomplishment behind you--the highlights of which I need not belabor for this well-informed group. The programs which the Division inherited and developed and those which you initiated have

neatly complemented the activities of the Institutes and have played a significant part in strengthening our national potential for biomedical research. It's a rare fifteen-year-old that can match that level of accomplishment.

Progress has sometimes been slower than you, or the rest of NIH, would have liked. You have had occasional temporary set-backs but these have not deterred you or diverted you from your steady course. There may be future delays and detours along the road but I am confident that you will surmount whatever obstacles you encounter and that the process of refining and adapting your programs to meet both scientific and societal needs will continue in the orderly manner in which you have managed it in the past.

Edward Young, the 18th century English poet whose sombre works gave rise to a school of 'graveyard poets', wrote that

"Old age will come; disease may come before;

Fifteen is full as mortal as three score."

But it has also been said--more recently and more optimistically--that "when you are young and strong, they can throw you down and the harder you hit, the higher you bounce." I see no prospect of anyone wishing to throw you down--and I would certainly seek to prevent that--but I am comforted by the conviction that you have plenty of bounce.

I hope and expect that the past fifteen years are but a prelude to the next during which the Division's new programs will mature and the scope of research resource support will broaden--and that it will be evident that,

in the words of Emily Bronte

"Fifteen wild Decembers . . . have melted into Spring."

It is a curious legacy of the organizational evolution of NIH that DRR is the only remaining Division, among a bevy of Institutes, providing extramural support for biomedical research. This has obviously not impaired your effectiveness with the scientific community nor your standing within the NIH family--and I am not aware that anyone is, or need be, particularly concerned by this anomaly. Perhaps it can be adjusted, in the interest of organizational tidiness, by the time the DRR reaches its majority. Meanwhile, I leave you with this thought from Mark Twain: "It is better to be a young June-bug than an old bird of paradise."



Welcoming Remarks 1/

by

Donald S. Fredrickson, M.D. 2/

Thank you Dr. Gordon.

If you are in the 14th floor auditorium or if by now you have overflowed into Wilson Hall or the gymnasium, NIH admits to being almost embarrassed by the turnout for the conference. Nevertheless, we are grateful and glad that so many of you could come today for what promises to be a very successful National Conference on Clinical Trials Methodology.

I must apologize briefly for the inconvenience that many of you may have suffered if you drove up to the front door today and found nothing but a great hole in the ground. We have inconvenienced ourselves, and all those who come to the Clinical Center, in the construction of the Ambulatory Care Research Facility, the first step in an essential modernization of this house. I think the ACRF is, or soon will be, further concrete evidence of NIH's endorsement of the importance of clinical research. Much of the work that eventually will be done in the ACRF will undoubtedly fit the definition of a clinical trial.

You know, as do I, that clinical trials are needed more and more as a means of ascertaining that those new treatment and preventive measures which are laboratory successes actually have a favorable impact on human

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1/ National Conference on Clinical Trial Methodology, October 3, 1977, Masur Auditorium, National Institutes of Health, Bethesda, Maryland

2/ Director, National Institutes of Health

health. The controlled trial gives us the opportunity to study not only immediate, but long run effects on outcome. It also has the capacity to reveal subtle effects that are not qualitative, but merely quantitative, differences between treatment groups. One of the most important lessons that trials, along with other epidemiologic studies, have taught us in recent years is that adverse effects of drugs and other treatments need not be considered as syndromes unique to the drug under study, but may manifest themselves as an increased incidence of a disorder that already occurs in the absence of the treatment.

Clinical trials pose a challenge to NIH because the number of significant questions answerable through clinical trials clearly exceeds our ability--indeed, the nation's--to plan, execute, and finance all the studies that are needed. During the last few years NIH has begun to take a careful inventory of clinical trials. The second edition of that inventory is now at the printers, and it will show that about \$114 million dollars was spent on clinical trials during FY 1975. The total cost of those trials, from their beginnings through anticipated dates of completion, will be something on the order of \$650 million dollars. The number of identifiable discrete protocols in 1975 was over 750, and the patient population involved was somewhat greater than 600,000.

What can we do about the need for more trials? More dollars clearly will not answer the problem alone, for human resources are limited. Two of the panels on this program are going to look specifically at utilization of human resources, investigators, and patients.

Perhaps efficiency would be a useful key word to describe many of the issues that are going to be addressed. Improved methodology will improve the benefit:cost ratio for clinical trials themselves. The published deliberations and recommendations of this meeting will constitute a useful guide for NIH in planning policy with respect to clinical trials and, we hope, it will also be a useful textbook for neophytes who may be planning their first grant or contract proposal for the execution of a trial.

Last week I was in Copenhagen and heard a somewhat melancholy report from the Dane, Professor Tygstrup, who is going to be the new Chairman of the Medical Research Council of Denmark, on his examination of the clinical trials literature. In his own field, gastroenterology, he found that over a ten-year period there were over 31,000 references to clinical trials, only about 1 percent of which were randomized. He established his own set of criteria for a "convincing" trial and found that, in a sample of about 100, none satisfied every requirement. One of the more distressing problems arose in examining textbook recommendations for the treatment of peptic ulcer. He noticed that 13 years of study had brought forth an increasing number of trials, all of which had shown that anti-cholinergic drugs were of no value in the treatment of the disease. At the same time, the recommendations for using these substances for treating ulcers were on the rise as well. Thus, a problem obviously remains in the area of translating results of clinical trials into practice, a matter of influencing the behavior of both physicians and patients. While it does not appear in the agenda for this meeting, this problem will remain to haunt us in the

future, and must be solved before the impact of our clinical trials will be as great as we wish it to be.

I do welcome you here, and hope again that you have a very successful conference. Before you begin, Dr. Earl Chamberlayne, of the Fogarty Center, has some announcements to make concerning housekeeping aspects of this meeting.



7 1

# NUTRITION EDUCATION

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HEARINGS  
BEFORE THE  
SUBCOMMITTEE ON DOMESTIC MARKETING,  
CONSUMER RELATIONS, AND NUTRITION  
OF THE  
COMMITTEE ON AGRICULTURE  
HOUSE OF REPRESENTATIVES  
NINETY-FIFTH CONGRESS  
FIRST SESSION

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SEPTEMBER 27 AND 28, AND OCTOBER 6, 1977  
WASHINGTON, D.C.  
NOVEMBER 7, 1977  
BOSTON, MASS.

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## IV

	Page
Dodds, Janice M., instructor in nutrition, Teachers College, Columbia University.....	287
Erkel, Blanche, consumer.....	347
Goodwin, Mary T., senior nutritionist, Montgomery County Health Department, Maryland.....	362
Gordon, Chris, Southern West Virginia Regional Health Council.....	384
Haas, Ellen, Community Nutrition Institute and Consumer Federation of America.....	305
Harty, Sheila, Ralph Nader Public Interest Research Group.....	232
Hershaft, Dr. Alex, president, Vegetarian Information Service, Inc., Washington, D.C.....	441
Hess, Laura J., director, Executive Office of Nutrition, State of Michigan.....	261
Jacobson, Dr. Michael F., executive director, Nutrition Action.....	297
Kinderlehrer, Jane, senior editor, Prevention Magazine.....	350
Marks, Bea, vice president, consumer public relations, Botsford-Ketchum.....	409
Mathews, Odonna, consumer adviser, Giant Food.....	321
Meringoff, Laurene, Harvard University.....	340
Petrie, Mary, WACAP, Danielson, Conn.....	313
Rowse, Arthur E., president, Consumer News.....	371
Ryberg, Dorothy, Northeastern Consumers League, Duluth, Minn.....	349
Schommer, Sister Carol, Office of Appalachian Ministry of the Catholic Diocese of Richmond.....	397
Schwartz, Loretta, journalist.....	240
Scott, Alice, national coordinator for school feeding programs, F.R.A.C.....	406
Shriver, Nellie, American Vegetarians.....	446
Voltz, Jeanne, food editor, Woman's Day magazine.....	334

## OCTOBER 6, 1977

Cardenas, Dr. Blandina, Commissioner of the Administration for Children, Youth and Families.....	551
Fredrickson, Dr. Donald S., Director, National Institutes of Health.....	539 ✓
Relic, Dr. Peter D., Deputy Assistant Secretary for Education, Department of Health, Education, and Welfare.....	527
Lashof, Dr. Joyce, Deputy Assistant Secretary for Health Programs, Department of Health, Education, and Welfare.....	495
Nielson, Dr. James, Deputy Assistant Secretary for Conservation, Research, and Education, U.S. Department of Agriculture.....	473
Foreman, Carol Tucker, Assistant Secretary for Food and Consumer Services, U.S. Department of Agriculture.....	454

## CORRESPONDENCE

Hesse, William R., American Association of Advertising Agencies, Inc., letter of October 5, 1977.....	488
---	-----

## ADDITIONAL MATERIAL

Austin, Dr. James E., lecturer in nutrition policy, Harvard School of Public Health.....	608
Barcus, F. Earle, School of Public Communication, Boston University.....	599
Berger, Marjorie, Alameda County Nutrition Council, letter of September 15, 1977, to Dr. Joseph Crapa.....	623
Gori, Dr. Gio B., Deputy Director, Division of Cancer Cause and Prevention, National Cancer Institute.....	564
Levy, Dr. Robert I., National Heart, Lung, and Blood Institute.....	588
McComb, Nancy N., Nutrition Policy Survey, American Association of University Women.....	630
Talerman, Mia, Respect for Living, Inc.....	626
Whedon, Dr. G. Donald, Director, National Institute of Arthritis, Metabolism, and Digestive Diseases, Department of Health, Education, and Welfare.....	578
Wood, Betsy, and Gullberg, Mary, Consumers Cooperative of Berkeley, Inc.....	617

STATEMENT BY DR. DONALD S. FREDRICKSON, DIRECTOR, NATIONAL  
INSTITUTES OF HEALTH ON NUTRITION EDUCATION

Mr. Chairman and Members of the Subcommittee:

You have heard today from Dr. Lashof and others that the Department places a high priority on nutrition and its educational components. At the National Institutes of Health, the same is true. However, we view nutrition education from a different perspective than most agencies.

The primary mission of NIH is biomedical research, and education of the public is a by-product of our efforts. It is important to keep this in mind as I address the four issues which you requested in your invitation. Those issues are types of information we convey, consumer population we reach, strategies we use, effectiveness of our current efforts, and our relationship with other agencies and organizations.

I think we can all agree, Mr. Chairman, that the vigor and productivity of the Nation's biomedical research is a necessary element to provide optimal health for everyone. The role of NIH is crucial in the development of the knowledge and dissemination of the research results which may benefit all people. As is illustrated in the first diagram, the principal focus of our attention with respect to dissemination of information is to other knowledge developers, the scientific community, practicing health professionals, and lastly to certain populations with special needs. These populations include pregnant women, children, patients, the aged, and those at high risk in all age groups.



Information is disseminated through a variety of mechanisms including literally thousands of medical and scientific journals, such as the Journal of the National Cancer Institute and the Journal of the American Medical Association, as well as through professional societies, workshops, and conferences. Still another method, as is shown in my second visual, is 35 publications dealing with nutrition. More than one million were distributed in 1976.

Public racks in almost 3,000 supermarkets, drug stores, and department stores are stocked with a selection of NIH publications. Although I will submit a detailed list of the publications, allow me to highlight a few of them :

- The hyperlipoproteinemia series, now nearing a total distribution of seven million, is available only to health professionals at their request. The set includes a handbook for physicians and dietitians accompanied by a ten-page supplement suggesting therapeutic diets for each of the five types of hyperlipoproteinemia.
- Facts About Nutrition has been supplied to junior and senior high schools, health agencies, physicians, supermarkets, and the general public. This booklet discusses what is currently known about good dietary practices, malnutrition, obesity, and nutritional requirements at necessary various stages in life. Approximately 250,000 copies have been distributed.

These efforts may be further illustrated by my third and fourth visuals.

The "Search for Health" news column is sent to 500 daily and small-town newspapers on a weekly basis. The particular column on view here addresses childhood nutrition. Five other columns also dealt with certain aspects of nutrition.

And finally, we have just begun an experimental series on the complexities of medicine entitled, "Medicine for the Layman," presented by our leading intramural scientists. This is a new and innovative method, and there will be ten other presentations dealing with a variety of subjects. The series are taped for possible use on public television.

It is important to point out that the educational program can only be developed if the data on which to base those programs are available. In the absence of clear data, it is difficult to recommend dietary practices suitable for everyone. What we do know is disseminated as quickly as possible, but we do not have a comprehensive program to test the efficiency and effectiveness of our nutrition education efforts. Specific projects within the Institutes may test effectiveness, but in general NIH efforts do not include costly evaluation procedures.

To provide a focus for nutrition research and to facilitate coordination, we have established the NIH Nutrition Coordinating Committee (NCC) with representation from all of the Institutes of the NIH as well as NIMH and NIAAA. Because of the key role of nutrition research in both health promotion and disease prevention, and because nutrition is an important trans-NIH issue, the NCC emanates from my office with a senior member of my staff as its chairman. This year the NCC sponsored

a Conference on the Role of Dietary Fiber in Health and is planning a national meeting in the Spring to review the current status of nutrition research and nutrition. The theme of the meeting will be "Nutrition in the Seventies."

The NIH also makes an important contribution to nutrition education through its training grants, awards, and fellowships. In fiscal year 1977, NIH funded \$3 million for nutrition research training.

Although many schools do not have nutrition departments, modern nutrition today is being taught by departments of endocrinology and metabolism, gastroenterology, as well as in special divisions of the departments of pediatrics, surgery, and medicine. This indicates that the subject does not lend itself to easy categorization.

A major contribution of NIH in nutrition education is carried out in clinical trials. For example, in both heart disease and cancer targeted populations are being exposed to nutrition education for the maintenance of health or treatment of disease. These programs are indeed successful and indicate that people are willing to change and improve their dietary habits when the information provided is directly applicable to them.

I want to stress that only two Institutes have specific mandates for information and education programs. These are the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI).

From the answers supplied by NIH to this Committee in response to your questionnaire, you are aware of the considerable activities of these two Institutes with regard to their development of nutrition education programs. The primary focus of the NHLBI program is prevention of cardiovascular disease through reduction of those risk factors which are amenable to nutritional modification or treatment. Other areas include the relationship of obesity to hypertension and research into modification of dietary habits.

The National Institute of Arthritis, Metabolism, and Digestive Diseases has also been active in nutrition education. Their target audience is broad based, ranging from school children to the elderly, as well as specific high-risk groups such as diabetics and patients with kidney disease. The Institute collaborates with nutrition and information resource centers associated with universities as well as TV and radio stations to run special TV spot announcements. One such effort is a soon-to-be-released one-hour film on diabetes. This film will be sent to over 600 teaching hospitals and academic medical centers. TV spots are periodically distributed to 700 stations across the country with a potential audience of millions of people. Surveys by NIH indicate more than half of these stations use the spots in their programs. Radio discs on diabetes were also sent to 6,000 radio stations. Companion publications on this subject are also available for the physician and his patient on meal planning for the diabetic.

NIH activity in nutrition education is further strengthened by



the efforts of the National Institute of Child Health and Human Development and the National Institute of Dental Research. These two Institutes have been especially interested in reaching parents and children. A considerable number of school mailings are made by the NICHD in response to requests for any one or all three of its excellent publications dealing with infants, children, and adolescents. This is also true of NIDR's popular pamphlet on dental care. The National Institute on Aging is planning a major conference on "Nutrition Utilization and Nutritional Status of the Elderly." Publication of the conference materials will be used by professionals and lay public.

The NIH collaborates with local and State government health agencies, the Consumer Information Service, and special interest groups such as the American Cancer Society, the American Heart Association, the American Diabetes Association, and the Candlelighters. We also cooperate with other Federal agencies and offices such as the FDA, CDC, USDA, OE, and HSA, the major delivery arm for Federal health care programs. In addition, the Office of Health Information and Health Promotion may provide a useful mechanism for the transfer of knowledge from NIH to other agencies and the public.

NIH also provides funds to other agencies and engages in joint endeavors including several Federal/State cooperative programs. NCI and NHLBI have provided suggestions to the National Center for Health Statistics on its nutrition surveys, and NHLBI will participate with the USDA and FDA in an attempt to augment pre-survey communications. For the last two years, NHLBI has provided \$300,000 to \$500,000 to support half the cost of the USDA nutritional composition laboratory

in Beltsville. NIH funds have also supported the development of a computerized program at the University of Minnesota, which allows for a rapid reading of the nutritional composition of a day's dietary intake. Jointly administered by the American College of Surgeons and NIH is a registry to collect and disseminate data on patients receiving total parenteral nutrition at home.

We are using the Communication Technology Satellite in an experimental program to link NIH scientists with practicing physicians in several localities. We have just signed a contract with the University of Colorado for a two-way face-to-face conference between a panel of scientists at Bethesda and some 400-500 primary physicians in Denver. Negotiations are also under way with the University of Kentucky for a similar conference.

In summary, Mr. Chairman, NIH as a scientific research agency does not attempt a large-scale education program for the general public for all diseases. But our efforts are serious and increasing. We will continue to give high priority to informing our primary constituency of scientists and health professionals. When the state-of-the-art reaches the right point and the data are conclusive, we will assist other agencies and organizations in carrying the message to the public, and will do as much of the job as we can. Our whole mission has the intent of assuring a healthy America.

I should also like to insert for the record at this time individual statements of the NHLBI, NIAMDD, and NCI. I shall also attempt to answer any questions you or the other members may have.

WILSON DAY ADDRESS <sup>1/</sup>by Donald S. Fredrickson, M.D.<sup>2/</sup>

Thank you Dr. Orbison, Mrs. Wilson

What Dr. Orbison did not mention is that I am now in danger of becoming the shopworn orator of Rochester. I don't know how many times I've had the opportunity to come here on special occasions. I'm honored to be asked again--especially to this one in memory of Mr. Wilson.

The current dilemmas of science--the rubric we're working under today--is an appropriate topic. What public or private institution doesn't have dilemmas? We don't want to be an exception.

The dilemmas take several forms. One of them, certainly, is always an economic one. There are strategic questions and there are philosophical issues. David and I will try to take these up serially. And we do really mean it: we are trying to avoid the pretension of being sages; we'd like to have participation from the audience.

I drew the lot last night to begin. I'm going to talk first about the financing of biomedical science in this country. I will take as the base for that economic view the institution that, perhaps more than any other, represents the nature of the funding of biological and medical research in this country. I'm going to give you, as background, a very quick historical economic resume because I think it's important for you to know where we are today--or at least where we seem to think we are--and how we got there.

<sup>1/</sup> University of Rochester School of Medicine and Dentistry, Rochester, New York, October 12, 1977.

<sup>2/</sup> Director, National Institutes of Health, Bethesda, Maryland

The NIH has the reputation for having a never declining budget and for maintaining a constantly expanding universe. Actually, that is no longer true. I come here not to lament that but to emphasise it as an inevitable reality because it means that during the next few years we shall have to make very important decisions that will affect the academic institutions that are carrying out the bulk of biomedical research in this country.

One can divide the economic history of NIH into three eras.

The NIH is 90 years old this year. We trace our history back to our ancestor, the old Hygienic Laboratory, which was established in a single room in the Marine Hospital on Staten Island in 1887.

During the first 60 years of its existence, it was strictly an intramural research operation. It is important to emphasize this because NIH is now, as it always was, preeminently a research establishment. It began with activities in nutrition and microbiology and quite early was given responsibility for biologics standards in this country. This parochial era ended in 1946 with the beginning of a Federal commitment to continue and expand the support for biomedical research begun during World War II. Until that time research had been supported primarily from private sources. There were very few foundations, the Rockefeller being the largest and the oldest having been founded around 1900. Those of you who decided to make your career in science about the time I did realize that the policy developed during the watershed years of 1945 to 1950 meant that you could actually do so without committing your family to certain penury. The Federal commitment was made at the end of a war in which the government



had found itself unwittingly engaged in medical research for military purposes. The Administration and the Congress were convinced by a variety of important people, such as Vannevar Bush and others, that it was time for this great country--affluent and an industrial giant--to accept the notion that it should be a part of the role of the government to accelerate this kind of science support.

This decision launched what I shall call the period of national expansion of biomedical research. That period goes from 1946 to 1963. It was such an important period that it still seems to linger in the minds of many as being representative of today when in fact this period ended more than 10 years ago. This period of national expansion had two phases. First came the strategy of sectoring--that was the subdivision of biology and medicine by disease or physiological system. This proved to be a very convenient political tool indeed, but, I think, not cynically so designed. What it meant was that the Congress and the Administration, in deciding to put money into this business, divided it up in ways that would ensure that it was going into research on the perceived health problems of the people. In addition to the National Institute of Health, which had been so named in 1930, there emerged, initially, a Cancer Institute, then one for heart disease, for mental health, and so on until there was a whole series of Institutes dedicated to diseases or physiological systems. This strategic sectoring went on for about 10 years, from 1946 to 1956. By the end of 1956 there were 8 such Institutes and the conglomerate had been renamed the National *Institutes* of Health.

During this period there was also a considerable expansion of intramural research on the NIH campus. The Clinical Center became kind of a biomedical

Bauhaus--a model for clinical investigation throughout the world. In this country, a very few places, like Rochester and Hopkins, had already begun to link the laboratory and medical people in ways that were very effective for developing the application of laboratory techniques to the study of clinical problems. However, the NIH Clinical Center, which opened in 1953, added a new dimension by its very mass, by the tremendous depth of basic science laboratories that surrounded it, and by the fact that, due in part to the draft, it was able to attract to Bethesda for periods of training a very large portion of that still small fraction of the medical school graduates interested in research. It was, for many of us, a revelation to discover what opportunities lay in the application of the scientific method to disease. From that Bauhaus came a very large proportion of the clinical faculties of American medical schools who paved the way for and were ready to participate in the second phase which I will call the phase of exuberant growth which took place between 1957 and 1963. This was the time when a national biomedical research establishment was created that was of massive and extraordinary proportions.

The average annual increases in the NIH budget during the seven years from 1957 to 1963 were over 40 percent. During that relatively short period, there was a ten-fold expansion in grants and in participants in research most of which was in academic institutions. Most of these institutions were too small. They weren't ready for this kind of largesse. Construction had also to be funded and every medical school in the country bears the mark of that period. There was also a generous increase in training grant allotments to academic institutions so that more researchers might be trained to permit this expansion to go on. Even international support was looked upon with

favor by the government, and NIH at one time had offices in Paris, Tokyo, and South America, so grand was the enterprise and so important was the American catalysis of a whole new era in biomedical research. By 1963, when the exuberant growth ended, the United States was unquestionably preeminent in biomedical research.

Now we enter another economic era which we might call an era of maintenance and selective growth. Certainly a very different period, particularly if you convert the funds available to constant dollars to reflect real purchasing power by correcting for inflation. This era also had two interesting phases. For the years 1964 to 1971 there was no growth at all in constant dollar terms. The maintenance formula, set out theoretically, was that there should be a 5 percent increase for growth, 5 percent for increased sophistication of research, and 5 percent for inflation--that is, an increase of 15 percent per annum. But actually it didn't work out that way. The outcome of the appropriation process during the years from 1964 to 1971 averaged about 6 percent or barely enough to keep pace with inflation.

During that time there were some interesting experiments with an expansion of the NIH mission. The Bureau of Health Manpower was transferred to NIH and it began to pay out the first capitation grants to medical schools and to look toward the creation of other kinds of health manpower. A Regional Medical Program was created by the Congress to extend the joys of the new discoveries to the health care system. It remained in NIH for about three years and was then moved out. There were some other changes in organization and some more Institutes were added.

From 1972 until this year, 1977, we have been in another phase which can appropriately be called the era of the mandate. This had an early neoplastic phase, during which the cancer conquest program was launched and the appropriations for the Cancer Institute were trebled within four years. This was partly due to a desire to expedite the conquest of cancer but I also suspect that it was partly due to a sense--on the part of many supporters of science and, perhaps, many participants in research--that the phase of no growth was getting us nowhere, that opportunities were being missed, and that an attempt to initiate some new phase of growth in this enterprise might be most successful if focused on cancer.

Well, there was renewed growth. The cancer conquest program has been criticized for too much preoccupation with the treatment of cancer, but I should note that it also allowed increased support for cell biology and immunology and virology and other areas that were about ready for further exploitation. There was also some growth in four other Institutes reflecting an expansion of interest, on the part of the Federal Government, in other areas. Research on environmental health problems, which now had its own Institute, was expanded. So was research on human development, and out of that came the National Institute on Aging--a new experiment in funding biological and behavioral and social science research on the process and problems of aging. The Eye Institute sprang out of the Neurology Institute. The Heart Institute added Lung and Blood to its name. This was--perhaps I should say is--an era in which the Congress became extraordinarily interested in specific diseases, some of them quite rare. Laws were written that specified that research should be greatly increased on Cooley's Anemia, on Multiple sclerosis, on Sudden Infant Death, on diabetes, on arthritis,



on Huntington's Chorea, on certain communicative diseases. The Congress became engaged, in an extraordinarily microscopic and detailed way, in determining how science ought to move throughout this particular period.

There were, however, also some unfortunate events. Some areas, because they were not so visible, or did not have popular appeal to societies of patients and their sympathizers, began to lose purchasing power. That was particularly true in the areas of endocrinology and metabolism, kidney research, and hematology. The General Medical Sciences Institute, set up to fund basic medical sciences, and also the Allergy and Infectious Diseases Institute lost about 10 percent of their purchasing power during this particular time.

Now we've come to what? Well, let's call it the phase of tomorrow until we see where we go from here.

This attempt to characterize the support of research historically has certainly offered very limited opportunity for useful induction. I think that biomedical research, which is now so utterly dependent upon Federal patronage, upon public monies, really makes apposite the utterance of Sir John Seeley who said that "History is really past politics and politics are present history."

To make a frame of reference for further discussion, we may ask three questions about the economics of biomedical research.

First, is it likely that we will return to a parochial period where resources will be derived primarily from private enterprise? I think the answer is most assuredly negative. The government is not uninterested or disenchanted with science. Its health priorities, however, do not place science first. Within the HEW, the priorities string out, as we see it,

with containment of health care costs coming first. The second is access to health care and the third is prevention. The attainment of knowledge is fourth--but not a poor fourth, because it is very clear that improved knowledge is one of the imperatives for reaching the other goals.

Are we headed for another period of exuberant growth or unselective expansion? The answer, I suspect, is equally negative although it is neither popular nor politically wise to say so. The reasons are basically economic but they're not the sole determinant in the competition for Federal funds.

There's a drop in school enrollment and it is predicted that university expansion will stop. We are currently experiencing an uncertain and somewhat unguided change in medical education patterns that temporarily deemphasizes subspecialization--which is a necessary component, an indispensable one, of vigorous biomedical research. There are signs that the small fraction of medical school graduates who are interested in research as a professional career is, at least momentarily, diminished. I think that we are also in a transition phase in the subject matter of scientific inquiry. We are groping for curriculums that will instruct more effectively for problems in the field or in the work place or in which population groups are the laboratory subjects. And we are groping for ways to attract young minds to the hitherto less romantic sectors of medical research. Even to suggest, however, that the promise of conventional research is diminished would be ridiculous. It has always grown in proportion to knowledge and, clearly, as the base has expanded, the needs and opportunities for useful and important research have continued to grow.

A loss of vigor in the thriving organism that was created during the earlier phase of expansion, and has since been maintained, would be very costly, not only to the United States but to the world. The thought that many developing countries will, in the foreseeable future, be able to achieve the sophisticated science capability created in some of the developed countries is unreal. Ours is an international resource that will have to be maintained with considerable care. Ways to do that by providing selective growth and harmless attrition are minimum objectives for this country for the present.

My third question is: If maintenance and selective growth are the future funding strategies, how are they going to be brought about? Let me say a few more words about that before I stop and let David begin. I believe the strategies are of two major kinds. One of them is political and the other is institutional. And of the two I've come to believe that the political is sometimes the more rational; at least it's more understandable.

What do I mean by political requirements, strategies, and maintaining the system? Although I believe that all science is humane and, I think, biomedical science is preeminently so, the latter simply must be exquisitely aware of society's expectations and needs in what it does. It must consciously strive to adjust to those expectations and needs in ways that don't diminish or destroy the essential process of discovery. Biomedical science simply must yield practical and useful development that subordinates palliation to prevention and that doesn't ignore the economic or other social consequences of any discovery or invention. We can explore this later this morning under the title of technology transfer.

This is a very legitimate and important demand, but this political problem must not be allowed to inspire research which approaches the grotesque. Some of you may have read, in a recent issue of Nature, William S. Hilliman's felicitous phrases. He says that political pressures may lead to two kinds of research--in addition to the real research which he defines as that based on the best judgment of capable scientists. The second kind of research, he says, is administrative research which is based on the premise that scientists can solve anything given funds, organization, and desire. And the third is defensive research which is sort of like defensive medicine. Basically, he says, these three types of research are analogous to real gold, fool's gold, and just quick silver.

Now what do I mean by institutional strategies? I include here all that is meant by the allocation of resources to foster real research in Hilliman's context. There are a number of people--those who are consecrated to systems analysis and other social critics, many in the upper bureaucracy--who believe that there can be far more rationalization of allocations for the support of science than I think is really possible. Politicians, gifted in the art of the possible, are not likely to be the ones who insist that this could be true. Too much zeal in this regard ignores a very fundamental principle and that is that the drive and the direction of the effective scientist is very much self-generated and self-contained. The expansion of knowledge also has its own dynamic and like a flood it will overcome all kinds of barriers that are constructed to divert it. You can harness and amplify these resources, which come almost for the asking from participating scientists, but you can't arbitrarily force them or change



them very successfully. An institution that is dependent upon that kind of individual, such as a university, also has a great capacity for accommodation and adjustment--and by that I mean that it knows lots of ways to beat the system in the interest of survival. A daily survival exercise is now performed by presidents, deans, chairmen, and members of laboratory groups trying to preserve the traditional goals and essential methodologies of science.

There is, however, a rational way of looking at the management of science and the allocation of its resources. I think that there are four major areas in which controls have to operate. One of these is the distribution between sectors of biology and medicine. One must allot funds disproportionately to various areas in accordance with some estimation of opportunity for significant advances.

Second, there is a question of distribution among activities within a field or discipline. This involves the balance between so-called basic science and applied; within applied, deciding whether to put more money into the development of preventives at the expense of attempts to make some small increments in therapeutic effectiveness or palliation of disease, and deciding how much money should be put into demonstration and control which are still legitimate areas of biomedical research.

A third area is mechanisms of support. Here we--the Institutes of Health and you, our constituent community--come to the need for a reexamination which must be skeptical of old traditions, except the essential processes of discovery which I think are understood and not deniable. In deciding how to allocate available funds, it is not profitable for a science administrator to try to define basic and applied research in any really

effective way. What we have to do is to understand the dynamics of inquiry itself and that takes into account how scientists really work. When you do that, you get down to a question of how much to put into small grants to subsidize an individual working on his own idea and how much do we put into large grants that support team approaches or departmental programs. Great aggregations of support also take into account an essential feature of the scientific process which is the important role played by entrepreneurs. There is an entrepreneurial aspect of science of which we have to take advantage in order to multiply and expand the capacities of single individuals. One of the things that we are doing now in Bethesda is to ask each of the Institutes to clarify its philosophy on the balance between the support of individual scientists and aggregate support. This is critically important in an Institute like the Cancer Institute which spends more than \$175 million a year in the support of comprehensive cancer centers. Are they really more effective in promoting discovery and stimulating good science? Does the rule of proximity really pay off? Do you increase and catalyze more effective exchange and cross fertilization by these investments? Answers will have to be found because the demands for expansion of that kind of support will exceed any rational expectations of budget increases in the coming year. It's very interesting and I won't take more time to discuss it today. It may be that these centers are the best means of engaging in what I call the marginal activities of science at the interface. Technology transfer and demonstration are problems that are not unimportant but we have to engage now in a searching evaluation of how well they really catalyze more effective research.

There is the matter of general research support. As you know, the Office of Management and Budget makes no secret of its view that the expansion is over and that these discretionary funds are no longer needed by the schools. My argument is that they are needed because without this lubrication a machine that isn't expanding will rust. This is a debate that goes on annually, and generally speaking, the Congress finally sides with the argument that this is an essential piece of the investment and restores it to the budget. Today we are spending about 2.7 percent of the total budget in funds that are given to the schools, under certain strict rules, for discretionary use. There is a belief that maybe the tough peer review process we engage in could some day fail to recognize the freckle-faced, red-haired student who couldn't possibly write an acceptable grant application but who does somehow come up with an idea that, if he could pursue it for a few years, might give us some new revolutionary turn or law that is the basis of real scientific movement. I believe in the system. Some limited discretionary funds are necessary but peer review is an essential screen for our project grant programs. The problem of accountability is exquisitely important for all Institutes.

Finally, there is the question of indirect costs--the costs that we pay the institution because we believe that the full cost of research ought to be subsidized by the government. But the methods of calculating indirect costs are leading to an ever increasing percentage of our total budget going to indirect costs and clearly a day of reckoning must be coming.

The fourth problem is that of manpower development. How many should we train? In what way, to maintain the system in a state of essential vigor? That could lead us into a very long discussion. But I have already taken more than enough time to simply lay out a structure and now haven't time to add more flesh to it.

## DISCUSSION

Question: Dr. Hamburg, would you like to ask the first question?

Dr. Hamburg: All right. I'm sure that the people in here have lots of questions for Don. I have one. What is the present state and what do you anticipate the future will be of the clinical research centers that the NIH has supported?

Dr. Fredrickson: The question is in regard to the clinical research centers that NIH set up around the country to make essentially free beds available for the pursuit of problems in clinical investigation. I think that there are two important determinants of how they will fare. One is that it is incumbent upon the institutions to strive for maximum sharing and efficiency in their utilization. There are universities where barriers seem to exist and utilization of these centers is confined to only one or two groups while others doing clinical research are seeking to have it paid for by categorical Institutes or by some other means. The second relates to the question that I raised before and that is the health of clinical investigation itself. There are a number of reasons, some of which I know you will touch upon, why clinical investigation is always, in a way, the toughest of all the kinds of biomedical research for a variety of reasons-- partly because it poses certain special technical and ethical problems but also because it is essential that we engage a sufficient number of creative hybrids who are willing to get the depth of training, on the one hand, in the laboratory and to retain their interest in clinical perspectives, on the other. These are the two things that will determine the fate of the



clinical research centers. The government is committed to this idea although it is possible that under National Health Insurance we might see some interesting change in attitude about financing clinical research or even some way to amortize some of its great cost. But I think that the provision of beds that offer the opportunity for patients to stay as long as they will continue to cooperate in important experiments is a basic principle that will stand.

Question: (not audible)

Dr. Fredrickson: Let me clarify the question. Under the selective growth principle or phase that we seem to be in, you ask what is going to happen in the long haul?

Question: (not audible)

Dr. Fredrickson: Well, you ask a question that I am probably no more capable of answering than are you. It is true that there will be regression in certain fields if support is withdrawn. Fortunately, however, the system is such that these shifts in emphases will not be so macroscopic but rather microscopic. By that I mean that rather than reducing all support for a discipline, there will be pieces of the activities which will have to be chosen, by some system involving much greater wisdom than perhaps any of us have, for emphasis on the microscopic level. An interesting thing has happened at NIH during the past five years: it has completely changed its internal administrative machinery for the management of its extramural programs. Formerly, the Institutes were organized to have maximum accountability and finesse in dealing with grants and contracts as instruments of support. They have now all converted to organization by programs. They have, in effect, been subdivided into mini-institutes. For example, the

areas of blood, lung, rheumatology, kidney, infectious disease, virology, and so forth, each have their administrative caretakers, their curators, who are keenly interested in those areas. The Institutes are thus subdivided in a way that makes it easier and more efficient to increase or decrease emphases, if we really want to use them as faucets. At the present time, the programmatic distribution of the Institutes is operating with faucets open wide because the controls are distal rather than proximal; in other words, there is so much good research, as judged by peer review, that cannot be funded that the level of funding has been left more or less constant across programs. But if this continues, program priorities will have to be used more than they are now to determine the degree of support. Clearly, a very important danger is that what you want to let atrophy today may be needed tomorrow, and I suppose the system to which I referred earlier, with its internal capacity for adaptation, will probably dictate how that will come about better than any contrived Federal policy.

Question: (not audible)

Dr. Fredrickson: Here is an important problem, because it is obvious that we must support certain areas of epidemiology, of knowledge about populations and of environmental control, far beyond what we have done so far. Indeed, the Congress has got us to a stage where we will have to adapt to new and greater demands in this area. The Toxic Substances Control Act

alone created a legislative requirement for expertise, for wisdom, for knowledge, that we simply cannot hope to supply with the existing numbers of people and their capacities. This is also true for the continuing movement toward more regulation. The problems of OSHA and regulating toxic exposures in the work place, and the mandatory requirements of the FDA for meeting certain standards, all mean that we simply must, somehow, get the best minds interested. We must move these problems toward the mainstream. Perhaps the best way to do it would be to call it molecular genetics, and after everybody is in the door, get them really interested. There is a relevance kick among some of our best scientists today. The Ames' test is an example of this. Ames, highly trained in sophisticated molecular biology, became interested in the question of what is in the potato chips that his kids were eating. Ames, as you know, decided that he didn't really know whether the ingredients on the label were toxic or not, nor did anybody else. He therefore devised new tests for mutagenesis, using Salmonella, to answer that question. This is the kind of re-orientation of interests that I'm talking about. Toxicology, for example, simply has no sex appeal and something must be done to attract some of the best minds to it. There is an extraordinary set of important problems here that need to be solved. I'm also talking about other aspects of environmental and occupational health. It's extremely important that we take advantage of these new emphases. But we must fight against a loss of the older, more conventional research problems in the process, those that still are at various stages of fruition and which must continue because it is from those basic areas that some of the essential answers for the practical problems will come.

There is a lot of competition. Take the Cancer Institute budget, for example. It is going to involve many problems, but one of these is going to be the charge that we are spending too much on the treatment of cancer and not enough on prevention. Well, if you look at cancer research, you realize how pitifully little we know about prevention. That isn't the fault of the Cancer Institute; it's just the state of the art. They can't even tell you what kind of diet you ought to eat to avoid certain cancers, because we don't know. It's a very difficult problem. You, society, will have to make some tough choices. You may have to leave off research that's expensive, that may give someone with cancer of the colon at age 50 five more years of life, in order to put more effort and more money into this darker, unexplored area of trying to classify the environmental hazards and to do something about them. In a period of the kind of maintenance funding we're in now, you have to make some tough choices.

Question: (not audible)

Dr. Fredrickson: I don't know whether Congress needs more education, and if I thought so I would not say so. All we can do is to point out to Congress what seems to us to be the proper proportionality of money for research in relation to total health cost. Then there will be economists, and there are plenty of them here, who will tell you the flaws in that argument. I also admit that we don't know how much research ought to be done. How do we set such a goal? There isn't any limit. There isn't any algorithm. The main thing is to try to keep up support for a vigorous attack, to realize that knowledge is essential. It's essential for ultimate survival, as much as anything else, because it will teach us something about adaptation



to a cosmos that we are constantly changing. I think Congress appreciates that. I think that Congress probably takes a longer range view than the administrations have in the past. But they are confronted with immediate crushing problems. They have got to hold down Federal expenditures, that is their philosophy, and I think that they are probably right. But they've got the welfare problem right in front of them. They've got costs going up 16 percent in hospitals and escalating Medicare and Medicaid. I don't think Congress needs to be educated very much about supporting research. I think they understand research. They understand basic research and they are very practical. But they do have to respond to all those constituencies, and they are, generally speaking, much more likely to be asked to listen to extreme views because on the fringes you have the most noise. It is very important that the great quiet center understands the political process and moves in to make its feelings and views about certain matters known. There has been a very dramatic demonstration of this in the problem of DNA legislation that we have just gone through--a really extraordinary example of the great center becoming vitalized and playing what I think is a responsible and important role in influencing legislation. Otherwise, Congress must listen to all those who clamor most loudly to be heard, and they are not always the most expert or the most reasoned. Usually they are not.

# DIET RELATED TO KILLER DISEASES, VIII

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HEARINGS  
BEFORE THE  
SELECT COMMITTEE ON  
NUTRITION AND HUMAN NEEDS  
OF THE  
UNITED STATES SENATE  
NINETY-FIFTH CONGRESS  
FIRST SESSION  
—  
OCTOBER 17, 1977  
—  
HEW OVERVIEW



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(II)

## CONTENTS

Statement of—	Page
Dole, Hon. Robert, a U.S. Senator from the State of Kansas.....	2
Forbes, Dr. Allan L., Food and Drug Administration, Department of Health, Education, and Welfare.....	19
Fredrickson, Dr. Donald, Director, National Institutes of Health, Department of Health, Education, and Welfare.....	13 ✓
Fullarton, Jane, Director, Office of Health Information and Health Promotion, Department of Health, Education, and Welfare.....	17
Kennedy, Dr. Donald, Commissioner, Food and Drug Administration, Department of Health, Education, and Welfare.....	14
Kennedy, Hon. Edward M., a U.S. Senator from the State of Massachusetts.....	11
Kretchmer, Dr. Norman, Director, National Institute of Child Health and Human Development, Department of Health, Education, and Welfare.....	31
Lashof, Dr. Joyce C., Deputy Assistant Secretary for Health Pro- grams, Department of Health, Education, and Welfare.....	15
McGovern, Hon. George, a U.S. Senator from the State of South Dakota.....	1
Richmond, Dr. Julius B., Assistant Secretary for Health, Department of Health, Education, and Welfare.....	3
Schweiker, Hon. Richard S., a U.S. Senator from the State of Pennsylvania.....	17

### APPENDIX

Kennedy, McGovern, Schweiker call for report on nutrition and health prevention.....	43
Detailed statement of the Public Health Service and departmental nutri- tion activities, submitted by Dr. Julius B. Richmond, Assistant Secretary for Health, Department of Health, Education, and Welfare.....	44
NIH legislative authority for human nutrition research.....	48
Evaluation of nutrition curriculum at nine selected medical schools.....	65



health policy together in his area, to try and set out some directions and set out some goals and what we might expect.

Dr. RICHMOND. Yes; we are looking forward to working with all the agencies with those responsibilities. I will be meeting later this week with Commissioner Perchuk to talk about some integration of our activities. Certainly the Federal Communications Commission, as you indicated, has an extremely important role to play.

I am sure Dr. Kennedy would have some comments about the important role that the FDA can play in all of this. We think that the time is ripe and that the leadership in each of these agencies is ready for this kind of integrated activity, and we will be exploring this very actively.

Senator KENNEDY. Dr. Fredrickson, we have been concerned in our Health Committee in terms of how priorities are being established at the NIH.

We hear during the course of these hearings about the importance and stress in terms of nutrition, and the kind of work that is being done. I know that is going to be developed further by my colleagues later in the morning.

One of the things we are all concerned about is how much pulling and hauling really can be done and how much leadership can be provided even by yourself, a man of unlimited energies and leadership and concern in this area, given the institutional problems that we face in terms of NIH with the various kinds of institutes.

I sometimes get a feeling that we put a lot of the pressure on you or we are pretty demanding in terms of this committee and others, in terms of trying to shape that institute. I suppose the real question is, how we can best and most effectively deal with the real kind of decision-making in the NIH, in the areas, for example, that this committee is most concerned about in terms of nutrition. And whether continuing to stress with you the importance that we place on that, whether that is really enough or whether we have to do something more.

#### STATEMENT OF DR. DONALD FREDRICKSON, DIRECTOR, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Dr. FREDRICKSON. I think, Senator Kennedy, I appreciate the inertial moment that you give me when you load me with these challenges because I can translate it, I think, to the next stage on the various Institutes. I think we are at a stage of understanding, a very limited half-stage of understanding that requires this kind of subdivision of the biomedical area into the forum that the Institutes represent.

But I think that we have in the last 2 years now begun even more successfully in this area of nutrition than any other to understand trends and how to work together. I think we can find a way to more effectively work together than we might do under any other organizational arrangement.

I am optimistic about that and I will be glad to develop the priorities and how we see them and how this is proceeding.

I don't think I need many more statutory powers to continue to make some progress.

Senator KENNEDY. Can I ask Dr. Kennedy, Mr. Chairman, how he sees the responsibility in FDA in this area?

I know you have a statement and I look forward to reading it. The idea of the coordination with both HEW and the Trade Commission is the area that I would be most interested in.

Health Science: Status Report\*  
(October 1977)

by

Donald S. Fredrickson, M.D.\*\*

It is a pleasure for me to be back briefly at the podium of the Institute. This is partly because my sense of guilt at leaving two years ago has been proved so unnecessary by David's far more skillful assumption of the Presidency. Today's program also suggests that IOM has captured much of the HEW bureaucracy and it's heart-warming to be among those come back to confess that it's easier to be a critic than a choreographer of the Healing Arts.

For my part I must talk about Health Science. It is not exactly synonymous with biomedical research or with NIH. Yet the NIH is so much of the whole that a summary of my perceptions of that organization will be the focus of my discussion this afternoon.

What are those perceptions of federally supported biomedical science? Perhaps there are two key ones:

First, it is a giant; but one whose myth casts a bigger shadow than does its present reality.

Second, it has passed through its childhood growth and entered an awkward stage of maturity. Its parents--the many public patrons--seek still to make the key decisions concerning its activities and further development. Yet

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\*\* Director of the National Institutes of Health, Bethesda, Maryland.

the nature of science is such that many of the key decisions cannot be made externally. The best that can be hoped for is the maximum of enlightened self-determination.

Let me first address the myth and the stage of maturity and get around later to the dimensions of the decision-making.

The economic welfare of biomedical research is inextricably linked with its major source of support, the NIH. By comparison with most federal enterprises, the fortunes of NIH have been good. But there persists in some quarters a belief that NIH is a cornucopia and that any diminution in its overflowing abundance is an aberration.

Allow me an historical analysis. Admittedly, it will have limited usefulness, for biomedical research is now so utterly dependent upon Federal monies that a comment by Sir John Seeley comes to mind. "History," said he, "is (merely) past politics, and politics present history." For Federally supported science that is an apposite observation.

We can readily distinguish 6 or 7 economic "eras" at NIH.

The first 60 of NIH's 90 years was a Parochial Period (1887-1945). There was no extramural research support. The Hygienic Laboratory, established in 1887 in an attic room of the Marine Hospital on Staten Island, and its successor, the National Institute of Health--so named in 1930--were simply the in-house laboratory of the Public Health Service. It is worth emphasizing that NIH is now, and has always been, first and foremost, a research establishment. It made notable contributions to research in nutrition--as, for example, in identifying pellagra as a



dietary deficiency--and in microbiology. In 1902, the Laboratory was given responsibility for the technical aspects of regulating the shipment of serums, toxins, and viruses--a responsibility that expanded into the Division of Biologics Standards which remained part of NIH until it was transferred to FDA in 1972.

The stage was set for the Era of National Expansion (1946-63) by the Public Health Service Act of 1944 which gave NIH the legislative basis for its post-war programs--and which began the major Federal commitment to the support of biomedical research. In addition to greatly expanded and diversified research of their own, the National Institutes of Health were given responsibility for continuing the extramural medical research and fellowship programs launched by the Office of Scientific Research and Development during World War II. There were two stages in the assumption of this commitment.

The ten years from 1946 to 1956 might be called the Period of Strategic Sectoring. Through a series of reorganizations and legislative actions, the National Institute of Health became a conglomerate of 8 categorical Institutes whose missions were focused on diseases and physiological systems, rather than scientific disciplines. Although cynics have often deplored the "disease" orientation taken by such a division of labor, it still makes sense in permitting secular oversight upon complex subject matter of unquestionably high public interest.

Until 1950 grant funds were still only a minor part of the NIH appropriations and even in 1956 more than a third of the total appropriations were for direct operations. The expansion of intramural research took a new direction with the construction, on the Bethesda campus, of the 500-bed

Clinical Center which admitted its first patient in July 1953. After the smaller Rockefeller Institute Hospital, I believe, the second hospital devoted solely to research. A felicitous combination of laboratories across the hall from the bedside, its provision of access of clinicians to intensive exposure to basic science and its grand scale, created from the Clinical Center a new *Bauhaus* of clinical investigation. An army of future professors trained in its confines would change their institutions to provide a similar ambiance.

The new organization and expansion of NIH activities set the stage for the Period of Exuberant Growth which, in conformance with biblical precedent, marked the 7 fat years from 1957 to 1963. With average annual increases of 40%, the appropriations\* grew from \$72 million (in 1956) to \$757 million in 1963. There was a 12-fold expansion in grants to academic institutions as the result of a deliberate Congressional policy to expand the U.S. capability for biomedical research by rapidly increasing

- . . . funds to support research projects;
- . . . federal assistance for the construction of research facilities (\$235 million in the 7-year period);
- . . . fellowships and training programs for research manpower;
- . . . and, to a more limited extent, support for research abroad (this grew from 92 grants costing \$190,000 in 1956 to 981 grants costing \$15 million in 1963).

This period saw the creation of the National Institute of General Medical Sciences, which is devoted solely to the support of extramural research and training in disciplines and fields that do not fall within

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\* Excluding programs no longer part of NIH (e.g., NIMH, DBS) and thus comparable with current figures.

the purview of the disease-oriented Institutes; and the Division of Research Facilities and Resources which, in addition to the construction program, supported the establishment of primate centers and administered the General Research Support Grants authorized by the Congress in 1960.

By 1963, the U.S. was preeminent in biomedical research. NIH even reached across the ocean, with grants to major foreign institutions, and had offices in Paris, Tokyo, and Rio de Janeiro, from which the seeds were sown that stimulated support for a new Renaissance of Biological Research in the developed countries of the world. But the geometric progression of 40% annual increases clearly could not be continued--in another 7 years it would have brought the NIH appropriations to \$8 billion! The Era of National Expansion--with its 10 years of Exhuberant Growth--had achieved its purpose and come to an end.

#### Era of Maintenance and Selective Growth (1963-197?)

It was then presumed that a period of slower growth should proceed. An attempt was made to promote a "normal growth strategy" of a 15% annual increase based on the rationale that it was necessary to provide

- . . . 5% for inflation

- . . . 5% for increased sophistication of research and the consequent need for more expensive equipment and more highly-paid technicians to run it; and

- . . . 5% for growth and expansion.

However, this approach was neither fully accepted by the Congress nor permitted by the Administration.

During the next 8 years (1964-1971), there were Congressional increases of more than 15% in only two years [1966 & 1971], a *reduction* of 5% in 1970 due to across-the-board cut-back legislation, and an average increase of a little less than 6% in each of the other five years. For the period as a whole, the NIH appropriations rose by 60% to \$1.2 billion but in constant dollars this was an actual increase of less than 6% spread over 8 years. From an economic or fiscal point of view, it was essentially an Era of No Growth (1963-1971) during which construction funds ran dry (in 1968), foreign grants were sharply curtailed, and the number of research grants began to fall.

Due to the effects of inflation and the changing character of research projects, the average cost of research grants rose by an average of 10% per year from 1963 to 1971--an experience that neatly justified the 'inflation' and 'sophistication' factors in the 15% 'normal growth' formula. Consequently, the maintenance of a steady constant dollar level in appropriations ultimately resulted in an annual decrease in the number of grants that could be funded. For the first 4 years (1963-1967) the number of research grant awards stayed fairly constant but then it dropped quite sharply from nearly 14,000 in 1967 to not quite 11,000 in 1971.

During the same period there began a decline in appropriations for training of new entrants and replacements in the research establishment. Subject of an annual tug-of-war between the OMB and Congress, NIH purchasing power for training--and hence training grants and fellowships--have declined to less than half of what they were 10 years ago. While, during this period, there was little growth in the extramural programs, the Federal interest in intensifying and extending scientific inquiry in many aspects of biology



and medicine was partly achieved by reorganization which, following the pattern of the earlier Era of Strategic Sectoring, set the stage for future expansion of certain activities. There were six major elements in the organizational growth of NIH during the 8 lean years.

. . . The creation in 1963 of the National Institute of Child Health and Human Development, was largely in response to President Kennedy's interest in child health. This was expanded, at the urging of NIH, into an Institute dedicated to the "Keynesian" or 'Womb to Tomb' approach to human development.

. . . The development, in 1964, of NIH's embryonic computerizing activities into a Division of Computer Research and Technology was undertaken to grow with the needs of the intramural scientists for sophisticated data processing and analyses.

. . . The establishment of an NIH component for Environmental Health Sciences (it became a Division in 1966 and an Institute in 1969) was the culmination of a protracted effort by the Public Health Service to get legislative authority for such an activity. When Congress finally approved, it insisted that the organization be part of NIH and that it not be located in the Washington metropolitan area--conditions neither of which were in the original PHS plan.

. . . The metamorphosis of the ophthalmologic component of the National Institute of Neurological Diseases and Blindness into a full-fledged National Eye Institute was initiated by the Congress in response to pressure from professional and lay critics.

. . . The John E. Fogarty International Center for Advanced Studies in the Health Sciences was created as a memorial to Rep. Fogarty--one who had been mainly responsible for the sustained Congressional initiative that made possible the Period of Exhuberant Growth. In addition to expanding the activities of the Office of International Research, which had existed since 1960, the Fogarty Center's authorizing legislation made possible an international fellowships program for bringing young foreign scientists to the U.S. and for sending American scientists abroad and it provided a site, on the NIH campus, for accommodating eminent foreign scientists as scholars-in-residence at NIH.

. . . The renaming of the Heart Institute as the Heart and Lung Institute, in 1969, was precipitated by a desire to head off the formation of a separate Lung Institute--in recognition of the growing importance of research on chronic respiratory diseases.

During this second Era of Strategic Sectoring, a couple of abortive efforts were made to expand the scope of the NIH mission.

The Congress responded to the recommendations in a report on Heart Disease, Cancer, and Stroke--prepared by a committee headed by Michael DeBakey--by giving NIH a supplemental appropriation of \$20 million for FY 1966 to intensify support for research in these areas and by authorizing Regional Medical Programs to combat these three so-called "killer" diseases. Responsibility for the latter service-oriented program was given to NIH--despite its reluctance.

Dr. DeBakey and his colleagues insisted, and Congress agreed, however, that NIH was the agency most competent to handle an activity that depended on the cooperation of

academic medical centers throughout the country. RMP was taken out of NIH in 1968, as part of a reorganization plan, and has subsequently died.

The major effect of the 1968 reorganization, however, was to elevate NIH to 'agency' status, with direct access to the Assistant Secretary for Health, and to transfer to NIH the National Library of Medicine, already located on the NIH campus. There also came in this period the Bureau of Health Manpower. Unlike RMP, it was welcomed by NIH on the grounds that research and training, being complementary activities in the academic institutions that already constituted the NIH clientele, could appropriately be administered by the same agency. In this case, however, the Bureau of Health Manpower was the reluctant bride and the relationship was not a happy one--perhaps largely because some of the training programs for which the Bureau was responsible did not, in fact, involve the same clientele as the other NIH programs. The Bureau was taken out of NIH in another reorganization in 1973.

#### The Era of the Narrow Mandate (1971 to 1977)

History does sometimes repeat itself. The sectoring and subsequent growth of NIH had its beginning, in 1937, in the creation of the Cancer Institute as a child and potential Oedipal rival of the then National Institute of Health. As one of the Institutes, NCI had long been the largest, but in 1971, the beginning of what can be best described as the Era of the Mandate began with a campaign in both Congress and the Administration to mount a War on Cancer.

In 1971 the Cancer Conquest Program was launched. The benign (non-cancerous) portion of the biomedical community was wary, but some accepted this initiative as perhaps the most practical way to avoid the potentially disastrous effects of a stagnation in research funding and a simultaneous demand for more research to be done on more health problems. In FY 1972 there was a 62% increase in the Cancer Institute's appropriation and increases averaging 15% for the other Institutes--for an over-all increase of 24% in the NIH appropriations. This rate of increase for the other Institutes was far from maintained, however, and the disproportionate growth of the National Cancer Program and the unique arrangements enacted for its administration gave rise to fears that this pattern of growth might prove malignant. These fears were not realized. The trebling of Cancer funds during the program's first four years (\$233 million in 1971 to \$692 million in 1975) had an important affect in permitting needed growth in several basic disciplines then ripe for expansion: genetics, immunology, cell biology, virology, areas of relevance not only to cancer but all of life science and medicine. During the four years 1971-75, when the inflation in biomedical research costs was 29.4%, the increase in constant dollars for the Cancer Institute was 132%. Three other Institutes grew in that time: Environmental Health Sciences by 38%, the now National Heart, Lung, and Blood Institute by 30%, and Child Health by 16%. Three others (Eye, Dental, and Neurology) held their own. But the purchasing power of Institutes underwriting research in important areas like endocrinology, hematology, kidney and infectious diseases, and several of the basic sciences underlying all of medical research suffered a capricious selective attrition.



Matters worsened as those with vested interests in numerous other diseases, rare as well as common, perceived scientific neglect of their particular causes and sought remedies through political action. Congress responded in a crescendo of actions between 1972 and 1974, and:

. . . passed a bill renaming the National Heart, Lung, and Blood Institute to give special emphasis to blood diseases and blood bank problems;

. . . changed the name of the National Arthritis and Metabolic Diseases Institute to the National Arthritis, Metabolism and Digestive Diseases Institute with an appropriate shift in program emphasis;

. . . passed the Cooley's Anemia Control Act; and

. . . created a Commission on Multiple Sclerosis to make recommendations on what should be done about that disease.

The National Institute on Aging--created in 1974, like the Eye Institute six years earlier, in response to pressures--has taken over the Center for Aging Research from the Child Health and Human Development Institute but has a much broader mission which includes the social science and behavioral aspects of aging and caring for the aged. In that same year, the Congress also passed the Sudden Infant Death Syndrome Act and a bill creating a Commission on Diabetes which also directed the Arthritis Institute to appoint an Associate Director for Diabetes. This Commission created a plan and gave birth to a public Board to oversee its progressive implementation.

In 1975, Congress added "Communicative Diseases" to the name of the Neurology Institute and created a Commission on Arthritis and a Commission on Huntington's Chorea.

The strengths of the admonitions have frequently exceeded the appropriations of new resources for the "disease-of-the-month" mandates. This, I view, as a sign of awareness on the part of the Congress that it is one thing to call loudly for discovery and another thing to send out more and more ships without charts.

What every reasonable party to all of these transactions wants is assurance that the capacity for exploration be kept strong and the ultimate destinations be sensible and in the public interest.

In regard to the first, three questions may be asked about the immediate economics of biomedical science in America:

*"Is it likely that we will return to a parochial period, where resources will be derived primarily from private sources?"*

The answer is most assuredly negative. The Federal Government has not become disinterested in or disenchanted with science. Its short-range health priorities, however, do not place science first. Immediate problems have higher priority: health-care cost-containment, access to care, and full utilization of existing modes of prevention. If acquisition of knowledge is last, it is not a poor fourth, for the need for improved knowledge is one of the imperatives in achieving the other goals.

*"Are we headed for another period of exuberant growth or unselective expansion?"*

The answer, I suspect, is equally negative, although it is neither popular nor politically wise to say so. The reasons are basically economic, but not solely matters of competition for limited Federal funds. A drop in school age children will bring curtailment of university expansion. We are currently experiencing an uncertain, and somewhat unguided change in the pattern of medical education which de-emphasizes subspecialization, a necessary component of vigorous biomedical research. Although medical school enrollment has increased 50% in the last 10 years, the scientific endeavor in the academic health centers has not expanded in any like proportion. There are clear signs that the always small fraction of medical school graduates interested in research as a professional career is, at least momentarily, diminished--and one reason is deep concern about the stability of support for such a career. We are also in a transition phase relative to the subject matter in health research, groping for curriculums that will better instruct for problems in the field, in the workplace, or where populations are the laboratory subjects. And we are groping for ways to attract young minds to these hitherto less romantic sectors of scientific inquiry, which desperately need further development.

The Cluster Reports of the President's Panel on Biomedical Research fairly state the paradoxical aspect of this "cooling off" of the scientific endeavor. The promise of "conventional" research is not diminished by other demands but can grow in proportion to an ever-widening knowledge base. A loss of vigor in that capability for inquiry created during earlier periods of expansion can prove very costly to mankind. Ways to maintain it that provide selective growth and desirable compensatory attrition must be our minimum objectives.

*"If maintenance implies increasing selectivity, what are the future funding strategies?"*

The answer to this question is a compound one. One part I would consider as the strategies of science in society--the political imperatives. The other I would call the institutional strategies, which concern the allocation of resources for conduct of scientific inquiry.

I believe that all science is humane in its objectives. Biomedical science is pre-eminently so, but its subject matter requires it to be exquisitely aware of its patrons' expectations and needs. And it must consciously adjust to them in every way that does not destroy the essential process of discovery. There must be practical, useful development emerging from health science. These inventions must subordinate palliation to prevention and not be offered in ignorance or indifference to their economic or other social consequences. It is perhaps too much to expect of each individual scientist, but their leaders must hear and understand the expectations of the Commons. It is the imperative of "technology transfer," whose quintessential statement appeared several years ago in the newsletter, *Changing Times*. "When science finishes getting man up to the moon," it observed sarcastically, "maybe it can have another try at getting pigeons down from public buildings."

To get the pigeons down, NIH has made a commitment on behalf of its biomedical constituents to engage seriously the social responsibilities hidden beneath the jargon of "technology transfer," "technical consensus," "technology assessment," and "demonstration and validation."



It requires tinkering with the current and traditional means of handling information and its serial conversion to knowledge and to wisdom. Mrs. Culliton has deftly described our entree into T.A. in a recent issue of *Science* in terms so objective I could not tell whether she was panning or praising us. This is as it should be, and whether we are right or tugging science too near to the fire of value judgment, remains to be seen. I am persuaded, however, that there is a mid-ground between Cartesian disengagement and the conflict-of-interest represented by regulatory practices or health service commitments. Most crucial to all of these political or social strategies, I suppose, is the care to see that we do not exceed the limits of our competence, let alone the well-known inapplicability of the scientific method to many current problems.

Consummate among the social strategies are those related to proving that science is capable of self-governance in regard to the safety of its laboratory practices. The controversy over recombinant DNA techniques has been a profound and most disturbing experience for scientists, for NIH, the Congress and many well-meaning, if often tragically mis-led laymen. I suspect we stand now at the tail, rather than in the eye, of a storm of hysteria, but are too close to events to have a proper historical perspective. I shall leave this matter--and the remainder of social strategies--until question time. For I am anxious to outline the other aspect of Institutional Strategies.

This is the area into which fall many matters mentioned earlier, both in perspectives and recitation of the economic history of NIH. It is the concern with how to maintain the most effective scientific enterprise within the total resources that emerge from the social strategies. It is the

area where I suggested self-determination by scientists themselves must rise to the challenge of making enlightened decisions or priority selections, which many external to the system would like to make for them.

The application of systems-analysis to scientific administration is far more limited than many reformers appreciate. Indeed, demands for precision in priorities exceed by a great deal the capability for rational management.

One cannot ignore the degree to which the drive and direction of the effective scientists are unalterably self-generated and self-contained. The expansion of knowledge has its own dynamic--especially in the complex and still relatively primitive biosciences. This dynamic can be harnessed and enhanced but it cannot be successfully thwarted by seeking to divert it to arbitrary goals.

The major institutions for scientific inquiry--specifically, the universities--are likewise but reflections of the individual scientists. They have a great capacity for adaptation and accommodation and long experience in exercising it, for they must seek as well to preserve traditional goals and essential methodologies. A tolerance for institutional purpose and an understanding of the sociology of science must be integral parts of the funding strategy for research.

While there is thus a narrow limit to the rational management of science through the allocation of resources, there are four or five areas in which such an approach--and some controls--can, and should, operate.

. . . The first is in the distribution between sectors of biology and medicine, between different disciplines and diseases.

Allocations here should come from a blend of assessments of social need and technical opportunity. Today, the final action at this layer lies with the Congressional appropriations committees.

. . . The second is the distribution between applied research activities within a sector or discipline. Within this layer is concentrated the most intense interplay of external and internal forces. Suspicions of the intent of the Institutes or of the scientists themselves emerge in challenges to the apparent distribution of effort. These involve emphases placed upon:

- prevention
- diagnosis
- therapy or palliation
- validation through clinical trials
- demonstration and control.

It is here that selection of problems becomes most critical and most difficult. How does one choose between improving the life expectancy of someone with cancer today against the prevention of cancer tomorrow? Different perspectives offer different decisions and each must be tempered by the expert's clouded estimates of the probabilities of success.

The pressures for external participation or domination in these selections is intense, and the capacity for this is extremely limited. If the experts must decide in the end, their permission to do so will rest upon the conviction they convey that they are sensitive and unbiased. The same applies to demands for coordination of research on problems where progress has blurred boundaries between traditional sectors of biology and medicine. It is here that collective direction is given its severest test. The Institute arrangement of NIH has enormous advantages and great strengths. It represents, however, a very superficial grid placed over a subject having fundamental unity at its depths. Its contours change through forces stronger than administrative convenience.

. . . The third institutional strategy is the allocation of funds between different mechanisms of support. I am of the conviction that somewhere here lies the solution to the cryptic puzzle of what is "basic" and what is "applied" research. Upon the allocations arising from that solution also rest the internal strength of any science.

The best approach to this problem, I am also convinced, lies through an appreciation of the sociology of science, and a disregard of some of the distinctions existing among the instruments by which research is supported. For example, the word "center" may have some local values but at NIH it has lost all significance in defining how if not why an organization is being supported as a whole.



To me there are, in fact, two kinds of grants--small grants and large grants. The first support a scientist and the basics he needs to pursue a goal which he has initiated. It is in the nature of science, as in other pursuits, that some individuals are entrepreneurial and will exercise greater creativity in larger settings. These, whether partnerships or "sections" or "larger laboratories," may thrive best under "program-projects" or other forms of larger grants.

The concept of a "center" is that of a larger aggregate of activities for which the rationale is usually that of bringing diverse disciplines together for purposes of cross-fertilization. One cannot deny that proximity is relevant in insemination, but so are gender and the presence of butterflies and other vectors. Size alone can sometimes lend a large movement of inertia to centers which tends to displace excellence as the principal criterion for award of continued support. It is also possible that, rather than in the degree of higher scientific achievement they promote, the value of certain centers lies more in permitting certain ancillary activities such as demonstration and technology transfer to take place. This gives rise to questions about the boundaries between health science and service which are inherent, particularly in the plural mandates of some of our Institutes of Health.

I do not know the answers to all of these questions. In years of maintenance or selective growth, however, they are the stuff of certain fundamental decisions which the NIH cannot escape. Indeed, in latter day organizational changes most of our Institutes have "gone programmatic" in ways which permit a better confrontation of the issues.

. . . This is also true for a fourth set of strategic decisions, and a fifth; the matters of indirect support to institutions and the training of research manpower.

The government has consistently supported the concept of cost-sharing to a degree and recognized that true costs to the institutions for supporting research are reimbursable. In maintenance years, however, it is inconceivable that the proportionality of these indirect costs to direct ones shall continue to rise.

General Research Support grants are discretionary funds allotted to institutions in proportion to the amount of research they conduct. These now represent about 3% of the total spent upon research. NIH believes these funds are critical to maintain the efficiency of a complex machine. The OMB, on the other hand, has consistently maintained that "now that expansion is over," such funds are no longer needed. Congress has so far contradicted this latter view, and a declining amount has been maintained in the budget for this purpose.

The exceedingly important subject of manpower training deserves more time than is permitted here. The NAS report of its second year's study of this problem and its recommendations to NIH and ADAMHA will shortly be public. It will be followed by a formal NIH response.

The current NAS/NRC report recommends a continuing decrease in predoctoral training in the basic biomedical sciences and that "identification of specific basic biomedical science . . . be eliminated from the NIH announcement" so that awards would be made solely on the basis of merit without regard (with the

exception of biomathematics and epidemiology) to the discipline in which the applicant will be trained. This procedure would have the effect of precluding the use of predoctoral awards to stimulate training in a particular field of interest to a categorical Institute.

The number of postdoctoral awards recommended, though constant, is 15% lower than the number awarded in FY 1976 and, here too, it is suggested that awards be made solely on the basis of merit "since field-switching is very high and the employment evidence is not sufficiently conclusive . . . to be the basis for science policy decisions."

There has been a steady decline during the past five years in the number of physicians receiving NIH support for research training in the clinical sciences (4,726 in FY 1971 to 2,800 in FY 1976--a 40% drop). The NAS/NRC report recommends that the FY 1976 level be maintained. But NIH is much concerned about the need for additional manpower for clinical research which is the bridge-head for the transition from laboratory research to application.

The report also recommends "that NIH . . . expand the program of health services research . . . at a rate of 10% per annum through FY 1981." While there is clearly a need, and at present, no viable Federal focus for such research, the extent of NIH responsibility for--and, indeed, competence to manage--health services research must be resolved before it gets more deeply involved in such training programs.

A related question, not dealt with in the NAS/NRC report, is training for service in which some NIH Institutes have, in the past, been indirectly involved as a spin-off from their research-training programs. Such involvement has been discouraged as lying outside the NIH mission--and, indeed, its legal authority--but the question may need to be reexamined in the light of NIH's renewed responsibilities for demonstration (i.e., quasi-service) programs.

To sum up, I have traced the economic history of NIH to provide perspectives for the decisions of today and tomorrow about support of biomedical science.

NIH has gone through 3 main phases during its first 90 years:

- 60 years in a Parochial Period when it was simply a Federal research establishment;
- 17 years in an Era of National Expansion; and
- 13 years in an Era of Maintenance and Selective Growth.

I have then discussed my views of the anatomy of a Low Growth Funding Strategy.

The agenda is complicated and both social and technical issues abound. Those who conduct biomedical research have felt the edge of criticism attendant upon the continuing appraisal of health and medicine. They have also shared in the orgy of introspection this has induced. The scientists will respond appropriately, I think, for their concerns share an identity with the public interests.

No doubt, society will continue to set mandates for biomedical research--as patron, it has the right of allocation. We who administer those funds will seek to arbitrate and interpret. All this will determine the rate at which science progresses. The eventual destinations to which research in the natural sciences will lead us, however, will not be determined by much of our conscious direction. Our vanities need to take note of that.



OPENING COMMENTS BY DONALD S. FREDRICKSON, M.D.  
DIRECTOR, NATIONAL INSTITUTES OF HEALTH  
at the  
INTERNATIONAL MEDLARS POLICY ADVISORY GROUP MEETING  
NATIONAL LIBRARY OF MEDICINE  
OCTOBER 27, 1977

Good Morning ladies and gentlemen. It is a great pleasure to be able to greet you and echo what Dr. Cummings has said.

How important has been the growth--and how significant that now there are ten nations in this network of information which is so extraordinary in its importance and in its achievement.

We have had a delegation from the Soviet Union this week. Many of you know the chairman of that delegation, Dr. Venediktov. Yesterday in discussing information, he gave voice to his anxieties that we really are one stage behind in information handling. MEDLARS is remarkable, he said, but it is old fashioned and what we need now is information on what is going on exactly at this moment and what is going to go on tomorrow.

Just keeping up with the very recent past has been difficult enough, and I wonder whether we shall ever really do that to our satisfaction, let alone accomplish some kind of future projection of science yet to come. The world of science grows closer together. It is this operation, this kind of arrangement, that is the structure which makes the whole greater than the sum of its parts. I think that, in a way, the manner in which you have made MEDLARS the success that you have, is

the best measure of science as a world-wide entity as opposed to a rather small national operation. You are truly the internationalization of science in every way.

I cannot tell you much about information; you can tell me much more. I can only tell you a little bit about where we are in the United States in what I would have to call the social strategies of science. These are not very different from your own countries. In the past five years, we have had more exchange, more criticism, more anger between science and the rest of society primarily because of something tangential to the course of biomedical science--the cost and inadequacies perceived in the health care systems which lie adjacent to these scientific activities.

One of the critical strategies in the United States has been an attempt to determine whether science is, in any way, responsible for many of the perceived problems in the health care systems. It is a difficult determination to make, very difficult for scientists certainly to make, and not easy for others who are external to it. In examining one possible way in which we may have a lag between invention and utilization, we have decided to try to see if there is some way that science can move just a little closer to the border between service and inquiry and to serve in this matter, of what has come to be called in this country "technology transfer": Now it is jargon, just as is "technology assessment"; but underneath, there is an implicit need for some change

in the method of handling information that arises from scientific development.

Briefly what I mean is this: there is a traditional process in which you are experts. You know as well as I, that something is discovered or work is done in the laboratory and eventually it is recorded. It goes to a journal where it will usually be reviewed, and we hope always carefully and objectively. It then may be revised or at least it will be approved, and eventually it will be published. Time lag is usually in the order of a year or two between actual accomplishment of the work and the time it is reported. That small tile added to the great mosaic will then lie and eventually become part of a further process of assimilation. It may stimulate others to extend it, or it will be confirmed, or there will be things that happen to it, but all in a rather laissez-faire manner according to the ancient dynamics of the system. Eventually if it seems to be worthwhile it will be part of a new resynthesis of knowledge which arises from like information adding new acceptable pieces to the old. Perhaps in another two or three years, it will become wisdom in the fact that it is encased between hard covers in a medical textbook.

Now one does not like to interfere with such a traditional process because its dynamism has come almost out of a natural law to a certain extent. We realize that you cannot accelerate that process easily without doing injury to it; and yet, quite frankly, it is not adequate for many of the social imperatives that surround scientific discovery when they begin to apply to actual practice and health.

There seem to be too many questions that go for many many years without resolution because there is no formal process to converge different opinions, to force some kind of consensus about the correctness or the incorrectness or the adequacy of that information. We know, if we can be patient, that this will take care of itself, although oftentimes it takes many many years before one really knows the worthwhileness of that kind of addition to information.

But now we come to a point where costs, increasing expectations, anxieties, so many other problems which are derivatives of the attempt to nationalize health care practices and to subject them to the regulation of public service organizations, simply finds this old traditional way of dealing with information inadequate. What is happening is that many sectors of society, many agencies of government, want to put their value judgments on a current piece of scientific expertise or know-how.

They have to do this for a variety of reasons because we are coming to a point, or have already arrived at it in some instances, where the fiduciaries will decide what they want to buy and what they will pay for. We are just beginning to encounter that in the United States; some of you have reached that somewhat more gracefully than we seem to be approaching it. But all of us, more or less, are trying to understand how one utilizes the continuing flow of scientific information as a part of a continuing process of regulating its use in medical practice. Engagement in this kind of value judgment, in setting medical care standards, is a very dangerous exercise for science. I will give you an



Illustration in just a moment of something I was on the phone about a few minutes before I came.

If the scientists do not know, if the experts cannot come to some agreement about what it is we know or do not know, then who else will ever be able to put together the fabric from which all these other decisions will have to be cut. And so we have been trying to raise the level of consciousness of our Institutes and our scientific community to realize that there are certain issues that cannot be left to the laissez-faire system to eventually resolve themselves. When there are answerable questions, or they seem to be answerable, we must construct some manner of approaching them, to force a consensus if we can, or arrive at one without force in a particular way.

There is nothing magic about this system at all; it simply consists of taking a good hard look at the available facts, but in the open. That is a particularly interesting aspect we find necessary in our society in America today. I know that there are some societies where this is looked upon with great concern in that it would seem to be disruptive and of no conceivable value. On the other hand, I know that many of you also have the same kind of concern, of how to engage known experts and the rest of society in such a process.

We have agreed among ourselves (we have not been forced by the government) to set up some kind of processes whereby we might try to see if we can

come to conclusions about these floating problems in a little faster way, and in a way that will address several requirements. One is that there must be enough known so that one can come to some mutual conclusion, or at least optimistically hope to do so. The second is that it must be in the open. We must be able to arrive at this in full view of that part of the public or press who wish to come along and watch. The third is that you must make sure the representation addresses the biases that exist around a given problem; that is very important. It is quite necessary to examine the polarizations which have arisen about an issue; and, although you cannot correct those, you can at least focus attention in the setting of discretion. Then of course you must work hard on the agenda; you must have very good people who are themselves optimistic and willing to attempt such an exercise. Finally there is an important requirement, and that is the way it is described and reported. I think that, unless this last is met, nothing has really occurred. It is an existential process just as is research itself; if it is not reported properly it never took place. The same is true of an exercise like this where we try to get down the facts and the manner in which decisions about the facts were reached, describe it in a way that will be useful to all those different experts. At least, we recognize in our society, the regulators, the consumer interests, the service organizations, and so forth who will want to take that kind of an opinion and use it for further decisions relative to healthier practices. It must be written up in such a way and in such vocabulary and vernaculars, that it is understandable to a range of audiences, both public and the experts of different kinds.

Recently we had such an exercise here, and we are beginning to see the good and the bad of it. We decided that the first subject would be the question of mammography and breast cancer detection. And the reason we did that was because we were already in a great controversy, within the community of cancer research and practice, about mammography, particularly in women of certain age groups. We set up a panel of about 20 people. We brought one or two people from abroad. We selected experts because, after all, it still takes experts to make these decisions. But we added to them what is now considered part and parcel of modern forum composition--somebody from the consumer's side and emphasis, several lawyers and so forth because they also add values. They can tend the fences that are surrounding experts within their own field and make them more cautious if nothing else. We obtained a professor of medicine from Yale as chairman who was a very fortunate choice, who had just the attributes needed. We had from Britain Archie Cochrane who is a veteran of such exercises.

For three days they sat, and they listened and they asked, and we had described from all sides of a long agenda the whole matter of breast cancer detection with particular emphasis on mammography. On the third day they broke up into small groups; and members of the public joined those groups. It became a kind of Commons exercise. It turned out not to be a Gerondist terror. It really worked. The process went on. People exchanged information fairly. Everybody was seeking to try to understand and to help reach some kind of decision. At the end of the day,

precisely on time, they heard their last piece of testimony and they came to some conclusions and developed verbally a set of positions, positions which were from the beginning only to be recommendations to the Cancer Institute in the way that it should further take care of some of the problems being addressed.

The Press was there in rather large numbers and throughout the three days there flowed a series of headlines which you could predict. The Press chose only those things that would seem to be the most scandalous or the most exciting and gave a very superficial impression to the public. The Television Networks came and, as is characteristic of our commercial television networks, completely failed to convey any meaningful description of what was really going on. And finally at the end there was a a press conference, and the most delicious topics were selected for the last set of headlines. The public, from the press coverage really learned basically nothing but confusion. It is for that reason that it is so essential to accompany this by some kind of follow-up presentation which can be of value to those who really want to know, who could tell others what really went on. It is a substrate for further journalism as is necessary.

There are some other things that have fallen out of that conference. One mistake we made was that the Cancer Institute had had a series of reviews of this whole project going on at the same time. One of those committees finished its report the night before this exercise took place and delivered its report for the first time at that meeting. In retrospect,



it would have been nice to have had that report given the night before because the organization, the beaurocracy, needed to have its reflexes tuned as to what was going to happen when the news arrived. The news of this particular report was that mammography, as with all new diagnostic techniques of far greater sensitivity, had created problems of false/positive diagnoses, which in the area of breast cancer can be rather tragic. The implication was that some scores of women had had mastectomies for lesions which were very small and about which there was disagreement on the diagnosis. There would have been no way, and certainly no propriety, in attempting to suppress that report. Therefore the fact that it was delivered the day of the meeting and became the center of controversy around it, I think we must accept as part of doing science and health in the open. On the other hand, it has created now an endless chain of questions--where do you go from here? what are the organizations going to do? what is medicine going to do in evaluating these important findings?

There are issues in this litigious society which will revolve heavily around the matters of malpractice; and in the end, we, as a scientific organization, will be caught in some charge of interfering with practice of medicine, of meddling in medical practice standards that other regulators would like to set, or of ignoring human rights and other obligations that surround the necessity of doing research completely in the open and in the proper way. I am sure that we will be able to handle this, but one must expect from technology consensus as any kind of

exercise like this, a great deal of perturbation or harmonics on the major theme which is being addressed. Yet, in the long haul I am convinced that science cannot withdraw from the process of determining the value of its own scientific information and conclusions. What is to be done with those conclusions has always been somebody else's concern, and should be. But we who speak for science and who bring the information to the hearth must stand there while it is dissembled or unassembled and put back in a form that is useful to society.

Underlying all this, you can see a new kind of need or set of needs for information handling which will continue to rise and never stop from this sort of exercise. There have been many decades of extraordinary scientific research in the laboratory, all of which had its ultimate purpose of moving some practical new inventions toward the benefit of man. I think it is inevitable now that we are at the point where those applications and developments are of such size and of such frequency, and have such importance on health care systems, it will be no longer possible to withdraw science as less a pastoral concern than it used to be in the days when many of us began our laboratory careers.

This is the particular information process that I wanted to discuss with you today. We have a whole other set of information problems that deal with safety of laboratory practices, with which all of you are more or less familiar and we have discussed, some of us, individually, with regard to Recombinant DNA techniques, as a classic example. But I think one unresolved problem is enough for a morning.

INTRODUCTORY REMARKS<sup>1/</sup>

by

Donald S. Fredrickson, M.D.<sup>2/</sup>

Our speaker tonight, Dr. Philip Leder, is a native Washingtonian. During his undergraduate years he was a summer student at NIH, in Martha Vaughan's laboratory. He received his B.A. degree from Harvard College in 1956 and his M.D. from Harvard Medical School in 1960.

From 1960 to 1961, he interned in medicine at the University of Minnesota Hospital. In 1962 he was once again at NIH, as a Research Associate in Marshall Nirenberg's laboratory. It was an exciting time, and his present and enduring interest in molecular genetics was firmly established. After a year (1965-66) at the Weizmann Institute in Israel, he worked in the Biosynthesis Section of the Laboratory of Biochemistry, NCI, and then in 1968 joined NICHD as Head of the Section on Molecular Genetics in the Laboratory of Biomedical Sciences. Since 1971 he has been Chief of the NICHD Laboratory of Molecular Genetics.

He has served as Vice President and President of the Foundation for Advanced Education in the Sciences, as well as Chairman of its Department of Biochemistry in the Graduate School. He is the recipient of a number of awards and recognitions of merit. Among the most recent was the NIH Director's Award in June 1976 for his work on the genetic code and his studies on genetic regulation.

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<sup>1/</sup> For presentation at the Mider Lecture, 8:15 p.m., November 2, 1977, Masur Auditorium, National Institutes of Health, Bethesda, Maryland

<sup>2/</sup> Director, National Institutes of Health

The programs of the Laboratory of Molecular Genetics are directed toward understanding the molecular processes involved in the transfer of genetic information from parent to progeny and from gene to functional product. Dr. Leder has made significant contributions to understanding the components of protein synthesis in bacteria. Most recently, his efforts have been directed toward understanding the organization and regulated expression of two sets of mammalian genes--those involved in globin production, and those involved in immunoglobulin production.

Dr. Leder's talk tonight is entitled: "A Close and Surprising Look at the Mammalian Genome."

Dr. Leder.



FOR RELEASE UPON DELIVERY



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20014

STATEMENT BY  
DONALD S. FREDRICKSON, M.D.  
DIRECTOR, NATIONAL INSTITUTES OF HEALTH  
ON  
RECOMBINANT DNA  
BEFORE THE  
SUBCOMMITTEE ON SCIENCE, TECHNOLOGY, AND SPACE  
COMMITTEE ON COMMERCE, SCIENCE, AND TRANSPORTATION  
UNITED STATES SENATE  
NOVEMBER 8, 1977

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(NIH) 78-1139, pp. 877-889.

Mr. Chairman and Members of the Committee:

In June 1976 the National Institutes of Health, with the concurrence of the Secretary of Health, Education, and Welfare and the Assistant Secretary for Health, issued Guidelines to govern the conduct of NIH-supported research involving recombinant DNA molecules. A number of scientific, administrative, and legislative events have occurred since that time which I would like to summarize for the Committee. Then perhaps a quick look at issues in evolving Federal policies for recombinant DNA research would be in order.

The new recombinant DNA technique has resulted in a profound and qualitative change in the field of genetics. Developments in genetic research, particularly in the last four years, open avenues to science that were previously inaccessible. Hypotheses and ideas that were not confirmed can now be rigorously tested. The understanding of basic biological phenomena has already been enhanced, and the promise of recombinant DNA research for better understanding and improved treatment of human disease is great. Further experimental data will be required to delimit the benefits that may be derived through this technique.

Some of the same scientists who foresaw the widening of the horizons of biology through these means were the first to express concern that they might be hazardous as well. The worst scenarios imagined microorganisms with foreign genes that could cause disease or adversely affect the environment if they should escape from the laboratory and infect human beings, animals, or plants. The Guidelines that resulted

were conservative, prohibiting all experiments with known risks. Where risks were unknown but potentially significant, appropriate standards were set to minimize those risks. Many recombinant DNA experiments have been conducted throughout the world during the past five years and are continuing. To date, no known hazardous organism has been produced in this work, and the risk of converting harmless organisms to harmful ones by recombinant DNA experiments remains speculative. Further work will eventually determine the limits of these speculative risks.

#### Scientific Developments

There is new scientific information developed over the past year that lessens concern over the possible environmental hazard from the research conducted under the NIH Guidelines. Dr. Roy Curtiss III, Professor of Microbiology at the University of Alabama School of Medicine in Birmingham, and others have demonstrated that biological containment measures--methods developed to weaken bacteria used in the experiments--would prevent these bacteria from surviving in a natural environment if they were to escape from the laboratory.

At a scientific conference held this past spring in Falmouth, Massachusetts, further evidence was given that the insertion of recombinant DNA into E. coli K-12 (the principal organism used in these experiments) could not transform it into a dangerous agent. Thus, risks from this cause appear minimal, either for laboratory personnel or the public at large. Dr. Sherwood Gorbach, chairman of the conference,

reported to me that there was substantial scientific consensus on this matter, not only among the molecular biologists in attendance but also among microbiologists who work with disease-producing bacteria. Proposed experiments involving insertion of recombinant DNA into organisms other than E. coli K-12 will also receive careful scrutiny before they are approved by NIH.

Much of the concern expressed about recombinant DNA experiments relates to the creation of novel organisms in the laboratory. However, additional evidence to be published this month suggests that the recombinations of DNA produced in the laboratory may be very similar to those that occur in nature. If further work confirms and extends the evidence presented by Dr. Stanley N. Cohen, a leading molecular biologist at Stanford University, then the concern about creating new forms of life will be put into a new perspective.

Mr. Chairman, I would like to submit for the record some documents describing in greater detail the scientific matters I have reviewed today.

#### Administrative Developments

The NIH Guidelines provide not only explicit instructions about permissible experiments, but also an administrative framework for their implementation. They set out the respective responsibilities of the principal investigator, the institution where the work is conducted (including the institutional biohazards committee), and the NIH initial review group (study section) which judges the scientific worthiness of the proposal. They also detail the responsibilities of the NIH Recombinant DNA Molecule Program Advisory Committee (or simply "Recombinant Advisory Committee," the technical body responsible for proposing the Guidelines), and the NIH staff.



The Office of Recombinant DNA Activities (ORDA), in the National Institute of General Medical Sciences, was established to coordinate the administration of NIH policies and procedures for safe utilization of recombinant DNA technology in research. Dr. William Gartland is Director of ORDA. Over the past year and a half, the implementation of the Guidelines by participants in this research has proceeded well. Approximately 110 institutions where NIH-supported research is taking place have established institutional biohazards committees, and approximately 228 projects are involved.

Over the past year and a half, administrative practices have evolved to deal with requirements of the Guidelines. One of the requirements is a means for interpretation. The standards in the Guidelines are very explicit about the conduct of permissible experiments. Still, questions of interpretation continue to arise and must be dealt with. Our determination to assure that the experiments comport with the standards of the Guidelines has necessitated a number of administrative delays in acting on research protocols. Where interpretation of the Guidelines requires exercise of discretion, an Executive Committee at NIH will review pertinent requests and advise appropriate officials and committees in order to expedite the administrative review of experiments.

Another area of difficult administration has been certification of new host-vector systems. These systems represent microorganisms weakened by various methods to prevent their survival were they to

escape from their specially contained environment in the laboratory. Presently, the Recombinant Advisory Committee must review all applications for new host-vector systems and recommend for certification those that meet the relevant criteria.

Because of the technical complexity of these certification decisions, the Recombinant Advisory Committee must frequently defer its recommendations for certification for several meetings in order to evaluate further scientific evidence. It was this latter circumstance that posed difficulties for the researchers at the University of California in San Francisco, who cloned genes in a host-vector system not approved at that time and therefore had to destroy their work and begin again once approval was granted. We have devised better lines of communication to ensure that investigators and institutions are kept fully aware of the status of their requests for certification.

There is no question but that experiments have been postponed and some scientific work delayed by the presence of the Guidelines and their implementation. At the same time, having embarked upon this course of self-restriction, NIH believes it must guarantee the integrity of the administrative safeguards and assure that due process is observed in implementation and revision of the Guidelines.

Mr. Chairman, I would like to insert for the record relevant documents on the implementation of the NIH Guidelines.

Legislative Developments

As you know, a Federal Interagency Committee on Recombinant DNA Research recommended in March 1977 that legislation be passed to extend the standards of the NIH Guidelines to all recombinant DNA activities in the public and private sectors. With your permission, I would like to submit a copy of that report for the record. On the basis of the recommendations, legislation was developed under Health, Education, and Welfare Secretary Joseph A. Califano, Jr., and an Administration bill was introduced in the Congress. The bill was considered in Congressional hearings, and other bills on the subject were introduced in the Congress. After several redrafts by the relevant Subcommittees, a Senate bill was reported to the Floor and a House bill was reported to the full Committee.

Although the two bills reported out contain many elements of the original Administration bill, a number of differences concern the Administration. For example, the Senate bill would give responsibility for regulation and the enforcement of standards to an autonomous regulatory commission. The House provisions are preferable because they appropriately place many of these responsibilities in HEW. However, the House version does establish an advisory committee that would have operating functions. These approaches, especially the Senate bill, would necessarily involve a greater administrative burden and some further delays and duplication in handling the highly technical matters involved in standard-setting and monitoring.

Mr. Chairman, certain of the principles embodied in the original Administration bill continue to serve as a model for simple legislation. At the same time, whatever legislation is enacted should avoid detailed listing of responsibilities that limit needed discretionary powers of relevant Federal officials and bodies. For example, subject to Congressional oversight, the Secretary of HEW, in developing and implementing regulations for recombinant DNA activities, should have flexibility to accommodate rapidly growing knowledge in the subject area.

Also desirable would be appropriate means to remove such regulation if demonstrated to be unnecessary. Legislation should facilitate maximum governance at the level of the institution where the research takes place, including responsibility for overseeing the conduct of these activities. Whatever the nature of the regulation, there must be careful regard for due process, full disclosure of information to the public, and a safeguard of its interests.

In the absence of legislation, recombinant DNA research in the private sector which is federally funded will continue to comply with the NIH standards as currently agreed upon by agencies involved. Elsewhere in the private sector, the pharmaceutical manufacturers



have publicly given their assurance of voluntary compliance. No evidence has been offered that any research in this country is being done outside the standards of the NIH Guidelines. The Federal Interagency Committee on Recombinant DNA Research will continue to serve as a forum for coordination and cooperation for recombinant DNA activities in the relevant Federal research and regulatory programs. The members of the Interagency Committee will continue to maintain close liaison with their respective communities, including agricultural scientists, biomedical scientists, environmentalists, labor unions, and private industry. For example, the Commerce Department is exploring means to ensure appropriate coordination of efforts in broader reaches of the private sector along lines developed in the past with the Pharmaceutical Manufacturers Association and the Industrial Research Institute.

#### International Activities

The Federal Interagency Committee will soon issue a report to HEW Secretary Califano on recombinant DNA activities in other countries, with recommendations for fostering common safety standards. I will provide copies to the Committee when that report is issued. Let me say that scientists abroad, as in the United States, have played a leading role in bringing potential hazards of recombinant DNA research to the attention of scientists, governments, and international organizations.

The issue of recombinant DNA research has been studied by national and international bodies throughout the world. In many

cases some form of control has been adopted, but nowhere has the research been totally banned. The United Kingdom and Canada have issued guidelines that differ in detail but are similar conceptually to the NIH Guidelines. Other countries are generally following the NIH or U.K. Guidelines, including Denmark, the Netherlands, France, the German Federal Republic, Israel, Sweden, and Switzerland. The European Science Foundation (ESF) has endorsed the U.K. Guidelines; the European Molecular Biology Organization (EMBO) has endorsed use of either the U.K. or the NIH Guidelines; and the International Council of Scientific Unions (ICSU) and the World Health Organization (WHO) have urged nations to adopt the principles that these two sets of guidelines embody.

As of the summer of 1977, there were an estimated 150 research projects using recombinant DNA techniques under way in Europe, 300 in the United States, and perhaps 20-25 altogether in Australia, Japan, and the Soviet Union. All appear to be conducted under some form of safety practices and procedures.

A number of national and international activities foster the monitoring of recombinant DNA research for purposes of safety and health. In the United Kingdom, the government's Health and Safety Executive will be responsible after October 1978 for ensuring that the standards of the U.K. Genetic Manipulation Advisory Group (GMAG) are followed in matters relating to safety of employees and the general public. The GMAG, consisting of representatives from the

scientific, public, and private sectors, reviews all recombinant DNA research projects for conformance to appropriate safety standards and practices. Similar advisory groups have also been established in other European countries, and efforts are under way to identify appropriate governmental bodies to ensure compliance with GMAG standards.

The European Economic Community (EEC) has legal authority under certain circumstances to enact policy decisions binding on its member nations. In this context, EEC has begun to examine scientific activities of member states to verify that the scientific and safety measures adopted are consistent and that private industry adheres to the same standards as the public sector. An EEC directive is currently under consideration which would require each member state to establish its own administrative mechanism to ensure that all recombinant DNA research is subject to national guidelines.

#### Proposed Revised Guidelines

In 1977 the Recombinant Advisory Committee, in accordance with its mandate in the original Guidelines, began the process of proposing revisions to them. Revisions were proposed, based on accumulated information on the effectiveness of physical and biological containment and on the biology of the hosts and vectors utilized in recombinant DNA research, by a subcommittee of the RAC which held open meetings in March and April. Following this, the proposed revisions were considered

and revised by the full Committee at public meetings in May and June. On September 1, 1977, revised Guidelines were referred to me for consideration and decision.

These proposed Guidelines were published in September for comment in the NIH Recombinant DNA Technical Bulletin. The Bulletin is a new NIH publication that will attempt to link investigators involved in recombinant DNA research both in the United States and abroad with the advisory groups and organizations active in this subject area. To provide further opportunity for public comment, the proposed revised Guidelines were published in the Federal Register on September 27.

Over the past two years, NIH has developed a roster of those in the public and private sectors who have followed and shared in the developing of NIH recombinant DNA policies. They have received copies of the publication in the Federal Register to ensure proper notice and opportunity to comment. All comment received from the public and the scientific community, including the private sector, will be considered by a public body, the Advisory Committee to the Director, NIH, at its December meeting. On the basis of the comments received and the reviews by the Director's Advisory Committee and the Interagency Committee, I will decide on the proposed revisions to the Guidelines and will issue a decision document explaining any modifications.



Mr. Chairman, NIH is preparing a description of the nature of the proposed revisions to the current Guidelines which I would like to submit for the record as soon as it is completed.

That concludes my statement. I would be pleased to answer questions.

WELCOMING REMARKS  
for  
SWEARING-IN CEREMONIES FOR DR. UPTON\*  
by  
Donald S. Fredrickson, M.D.\*\*

Some of you may remember that about ten years ago the renowned Isaac Stern appeared in concert in this very hall. I had occasion to chat briefly with the maestro following his performance. I asked him if reverberations from the marble covered walls of the auditorium gave him any difficulty.

Mr. Stern quietly responded . . . "It might be a problem if you have too much brass in here."

In planning for this ceremony, taking note of the fact that we would bring together persons of the rank of our platform guests--and that Tony D'Angelo and his 76 trombones would be playing for us--we took the precaution of sprinkling the cushions in the first 15 rows with heavy water--thereby avoiding the critical mass that Maestro Stern worried about.

It's in the nature of human endeavors that pledges become past due, and have to be renewed. This continuing renewal is especially important for the kinds of goals upon which this House was built and toward which the people in it daily direct their lives.

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\* As Director of the National Cancer Institute on Thursday, November 10, in the Masur Auditorium, National Institutes of Health.

\*\* Director of the National Institutes of Health, Bethesda, Maryland 20014.

The intent to understand, and eventually control, the diseases called cancer did not begin on what was, 40 years ago, a simple pasture in a place called Bethesda, Maryland. Yet today, by far the largest share of the world's resources devoted to this task are either used here or distributed from this campus. It is an awesome challenge and a great responsibility. And the person who has it today is chosen by the President of the United States.

You will recall that Secretary Califano at the President's request established a search committee to find the best person for the Directorship of the National Cancer Institute. This occasion marks the successful accomplishment of that task. We are here to witness the swearing-in of that person--the eighth to direct the National Cancer Institute. We are honored indeed that the Secretary and other high officials of the Department as well as three members of the National Cancer Advisory Board have joined us for this occasion.

The first National Cancer Program considered by the Congress was the posting of a bounty--just 50 years ago Senator Matthew Neely of West Virginia introduced a bill offering a reward of \$5 million for the discovery of a cure for cancer. He received so many purported solutions that he then turned to the National Academy for help in judging them. Ten years later, the National Cancer Institute Act was passed in 1937, creating a companion for the then young National Institute of Health. Both, then units of the Treasury Department, moved out together to Bethesda. Their relationship may have been a common-law one at first, but the union was legalized in 1944. The first of the categorical Institutes, and in recent times by far the largest of the Institutes, NCI has been one of the most productive and provocative of the colleges in this university.

The intervening years have seen more than a thousand-fold increase in their 1937 budgets for both NIH and NCI. At times the forces derived from their accelerating activities have been inevitably centrifugal; yet common purposes, common needs, and most of all common sense have kept us always together. And today, the NIH community is bound more closely together than ever before by the steady convergence of all biology into one broader discipline.

Of the biblical seven Directors who have preceded the incumbent to be formally installed today, I will mention only three: Kenneth Milo Endicott, the fifth Director, occupied this post when I was Director of the Heart Institute. This meant that our mutual home town of Canon City, Colorado--all of 5,000 inhabitants--was, for a brief moment, the unsuspecting health research capitol of the world. The third Director, Leonard Andrew Scheele, was a graduate of the University of Michigan and later became Surgeon General. The second was Dr. Roscoe Roy Spencer. Shimkin's history reads:

" . . . disaster struck Spencer when he testified before a Congressional appropriations committee that he did not think that an expanded budget for the NCI was justified."

This kind of modesty has not reappeared among the NCI Directors or for that matter among the Directors of the other Institutes.

It is my pleasure now to present our special guests and participants in this ceremony.

First, the Assistant Secretary for Health, Dr. Julius Richmond, who came to us from Harvard. Dr. Richmond has, in his person, ended the mysterious absence of the Surgeon General and in his actions is filling that important role -- Dr. Richmond.



Undersecretary Hale, Champion, until recently Vice President of Harvard, and now the unencumbered right arm of the Secretary -- Mr. Champion.

Elizabeth Upton adds greatly to the grace and charm of this unusual community. When we asked her husband yesterday if she should be called "Betsy" which most of us thought was her given name--his answer was that it depends on how formal the ceremony is to be--"If you call me Art, call her Betsy. If you call me Arthur, call her Elizabeth." -- Mrs. Upton.

In looking back on his Presidency, Thomas Jefferson said that "No duty the executive had to perform was so trying as to put the right man in the right place."

For the 1970's, that quotation has an unfortunately sexist ring. Otherwise it will forever express cogently the heart of the matter we are celebrating this afternoon--because in this instance the Executive has succeeded indeed in performing well this trying responsibility.

And now Dr. Arthur or Art Upton --

And finally--it is my special pleasure to present Secretary Joseph A. Califano, Jr.--whose unmatched intent to understand and master the system for which he is responsible has led him to thrust himself directly into the health care mechanism--Secretary Califano.

OPENING REMARKS  
GENETICS PUBLIC MEETING 1/

by

Donald S. Fredrickson, M.D. 2/

Twenty years--and about 4 Directorships--ago, I was a member of the "senior research staff" in the National Heart Institute. Two other young Turks and I had met at the Brighton Punch Bowl in Atlantic City in the spring and agreed to write and edit a book. We hoped to cover completely both the clinical and biochemical aspects of all of the phenotypically single gene defects recognizable at the time. We would leave out only the connective tissue disorders, which were then a formidably amorphous and arcane set of unhappy anomalies which only Victor McKusick had the patience to classify.

Otherwise it was our intent to assemble the most complete coverage of the inborn errors of metabolism attempted since Garrod's discovery of the concept in 1909. Many of the stars who were to preside over an imminent expansion of the many laboratory and clinical aspects of this field were recruited to describe the disorders occupying their particular interests.

The initial volume was a succes d'estime and this month the fourth edition will appear. It is vastly more complex, much wordier, and ever so much more informative than the first. I have now been working for two

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1/ Sponsored by the Public Health Service Genetics Coordinating Committee, December 7, 1977, Wilson Hall, National Institutes of Health.

2/ Director, National Institutes of Health, Bethesda, Maryland.

decades on a subset of these diseases and intermittently been writing and editing successive editions of this text. The experience has given me both an expert's critique and an amateur's unlimited admiration of the extraordinary resolution with which we presently are able to perceive this galaxy of inherited monogenic disorders of metabolism.

In relatively so short a time, the view has become simply fantastic. The progress was predictable, given the accomplishments of more fundamental research in genetics which preceded and continued during this same period. From the time of Mendel, if you want to go back to 1901--or only back as far as Beadle and Tatum's "one gene, one enzyme" idea--that would be 1941 to now, the general expansion of genetic knowledge will go down in history as one of the most important human intellectual achievements of all time. And it's continuing at full tilt, even omitting the ten thousand flowers predicted from study of novel recombinants.

Since 1933 there have been 9 Nobel Prizes awarded for discoveries related to understanding of the genome and the manner of its translation and transcription. Contemplation of the genetic code creates an awesome reverence. Not only for its universality, but for the ingenuity of nature in establishing communication between the most primitive beginning of life and the unimaginable species variation that is to proceed for generations beyond us.

Knowledge of genetics with practical implications is also growing steadily. The capacity to detect the bearers of mutant genetic messages having serious consequences continues to increase. They may be detected as

heterozygous carriers prior to child-bearing. The unfortunate conjunction of defective alleles derived from each parent, can be detected in utero, in a slowly growing number of diseases. By the same token, the proof that a fetus at risk is, in fact, healthy can be reassured by the same means.

Some genetically abnormal fetuses can be brought to term and the life of the child made more normal, or even nearly completely so, by appropriate and timely therapy--usually that aimed at tiding the child through a particular phase of development of until compensating mechanisms for adaptation have matured.

In some abnormal phenotypes, replacement of missing gene products works on a transient basis. Ingenious ideas to increase this capacity or to replace permanently the missing gene product are not beyond realization in the future.

All in all, the movement of new knowledge about genetics--from the more basic toward the more technological--has been dramatic, and in keeping with the best traditions and promises of biomedical research.

All the promise achieved thus far has been easy compared to its realization in the form of appropriate social usage of the technology acquired.

The Genetics Disease Act, P.L. 94-278, emphasizes this desire, not how to accomplish it. The law is a complex expression of congressional concerns that rise from all quarters of society. People do not fully understand all the purposes of genetic screening or other programs, and yet to not wish to miss any proffered benefits. The Genetics Diseases Act



poses a challenge to several Federal agencies to work together in the best interest of the public. It challenges the public to decide just which of its many interests in genetics it wishes to be served.

Helping to convert an important fund of information and knowledge to social wisdom is the major and difficult purpose of this meeting. It is my belief that you should strive to assess and describe clearly the technical limits of the subject. You must end by laying out the options without pretending to have completed the choice. You will need to offer your services to aid those who must arrive at the final choices. They will be political, legal, societal, and personal. Except for the last, the mechanisms for making decisions are poorly in place. But this meeting is part of the road toward their creation.

I wish you well.

## The State of Nutrition Research\*

by

Donald S. Fredrickson, M.D.\*\*

The President's Annual State of the Union message is a prominent feature on the political scene at this time of year. There seems to be an ever increasing number of exercises in Washington for examining the state of common, complex concerns. I was engaged in one yesterday having to do with the State of Genetics. There are some peculiar similarities between genetics and nutrition. I don't think that there is any intellectual achievement in the history of man that exceeds the growth of knowledge about genetics that has occurred between say, about 1940 in the Beetle and Tatum era, and the present--and this is leaving out the 10,000 flowers that optimists predict will result from recombinant DNA research. Yet, at the same time, there is a peculiar disjunction between the state-of-the-art in genetic science and its application. Now, as the Congress is engaged in a traumatic debate on abortion, we see exposed an uncomfortable number of political, legal, and public decisions that complicate the use of new knowledge. The genetic code is revealed and proves to be universal. Its translation to practical terms is more difficult. There are no universal social truths and none but statistical mechanisms to define the norm.

To a certain extent, the same is true in nutrition. The state of the science is extraordinarily healthy. At the same time the transfer of burgeoning new knowledge to practical ends—to help guide people to

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\*Presented at the NAS Food and Nutrition Board at the National Academy of Sciences, Washington, D.C., on December 8, 1977.

\*\*Director of the National Institutes of Health, Bethesda, Maryland, 20014.

health through wise choice of foods--is perceived to be a lost art. Many have sought--and until recently none have found--evidence of public nutrition policy or of Federal intent to create one. In the past several years, primarily through the action of the Senate's Select Committee on Nutrition, there has been an attempt to develop some Government policies that can be debated and, at least in part, adopted. What Carol Foreman has had to say today about the USDA was refreshing. It makes good sense now, in a country which has such extraordinary capacity in food production and has done so much research, to stop and see if we know enough to adopt some form of public policy on nutrition, and to converge the activities of our Departments upon common goals.

As pleasing as it is to hear the announcement of some "Federal intent," it becomes necessary to make some practical decisions. You heard Phil Handler speak earlier today of the feebleness of science when it is called upon to give incontrovertible answers to simple social and political questions. If we are to be carried away by a spirit of activism, it seems we must create some policies from incomplete data and perpetually unfinished experiments. As Ms. Foreman has earlier suggested, nevertheless, there is merit in settling for probability, rather than waiting eternally for certainty, in making some decisions on what is better to eat.

May I say a few words about the state of nutrition as a science? When I was Chairman of the Publications Committee of the American Physiological Society several years ago, I had many encounters with people

who would have to be called classical academic physiologists. Their common complaint was that physiology was dying. It was, and has been, for some time, but only in the sense of being a discipline a single person could wonder. Yet physiology is bursting out all over, its component parts have never been more robust, although now identified as membrane biology, biophysics, and many other sub-specialities. I think the same is true of the state of nutrition. There is no doubt that we have gone through several cycles in nutrition science in the past two decades. After the establishment of the macro-components of the diet, and the recognition of the essential micro-ingredients, such as vitamins and certain trace minerals, nutrition research continued to swell like a great river. But slowly I went underground, into the regions better recognized as biochemistry, into the specialties of physiology, genetics, even into the behavioral sciences. Old-fashioned nutrition became just that. Although unjustly condemned as being mere "dietetics," it has not had an easy struggle to keep honest, in an era when the media serving an affluent populace have had such an awesome appetite for new wonder diets and nutritional celebrities.

Meanwhile, by other names there have been many latter day achievements in nutritional research. Let me remind you of a few. There is the elucidation of what happens to Vitamin D, how it has to be hydroxylated to a hormone to control calcium and phosphorus metabolism, and how that information has improved our use of the vitamin in regard to such diseases as renal osteodystrophy. There has arrived an enormous amount of new information about the effects of nutrients at various stages of development, and how poor nutrition can arrest the growth of the brain, perhaps even determine the amount of DNA and the number of cells an organism will



have for the rest of its life, and otherwise change the genetic composition of an individual through early imprinting and other aspects of the environment. There continue to be fundamental developments in the busy old area of cholesterol and fat metabolism. The discovery of the membrane receptors for low density lipoproteins and their relationship to the control of cholesterol synthesis is one of the notable strides yet to be integrated into individual capacity for handling milk, butter and eggs.

The importance of additional trace elements like tin, vanadium and fluorides, silicone and nickel have been demonstrated, some have even been found essential for the growth and well-being of animals. We know more about the functions of other trace metals. Certainly we know a lot more about the carriers of nutrients. Many nutrients are absorbed and are transported in man—as had previously been known for Vitamin B12—by specific carrier or transport proteins. Examples are the apolipoproteins required for lipid absorption, other protein carriers in carbohydrate absorption and specific transport proteins such as the retinol-binding protein that transports Vitamin A. Someday these discoveries will illuminate crucial differences between individual differences in the speed and efficiency of the transport and utilization of nutrients by the body.

There have been many other fruits from modern nutrition research. Exposure of mechanisms of protein synthesis and its regulation cannot be carried out to levels too deep to tell us important things about protein and nutrition. Study of subcellular mechanisms has demonstrated how the liver responds to the influx of amino acids after a meal, or to the availability of essential amino acids in the diet, and that the synthesis

of enzyme proteins by the liver is more responsive to changes in the supply of amino acids than we had earlier imagined.

Contrary to previously held views, the plasma levels of amino acids are now known to be important in determining the availability of free amino acids to the brain. Synthesis of serotonin and some other neurotransmitters can be regulated by availability of amino acid precursors. This could be relevant to effects of nutrition on brain function that can be produced by amino acid supply during development and thereafter.

I think it is exciting to know that Vitamin K actually functions by carboxylation of glutamate residues of inert proteins like prothrombin, thus activating the proteins so that they may respond to blood clotting stimuli. This may provide the basis for better management of thrombosis and other undesirable clotting of blood. Reduction of phenomena to molecular terms rarely remains simply an artistic achievement, but eventually has practical merits that exceed our initial dreams.

I dwell on these things, perhaps excessively, because they bear on the questions of how much are we spending and how much are we doing in nutrition research. Many of the things that I have mentioned were rejected by some observers as not representing nutrition research in a recent analysis of NIH activities that we prepared for Senator McGovern's hearings. Obviously I disagree, but there are honest differences of opinion as to just what is nutrition research today.

Depending upon definitions, NIH is either spending somewhere around \$20 million, at the lowest estimate, or in the neighborhood of \$80 million annually on nutrition research, education and training. The higher figure is that suggested by the NIH Coordinating Committee on Nutrition, and I believe its estimate is fair. At either limit it is more than any

other agency. Is there a gap in awareness about such research and its importance? Yes, although it is not too serious a problem. NIH has a further great responsibility to ascertain whether the many scientific achievements in what it considers nutrition, as richly varied and highly promising as they are, also serve the public purpose and needs. Is there a gap in technology transfer in regard to nutrition? Yes, I think there is. At least, there are some symptoms of lag between all we are learning and what practical uses we know we are making of it.

The current debate about nutrition and nutrition research has been a very healthy thing for NIH. It has made us reexamine what our activities amounted to and to develop some methods for better coordinating them. Coordination initially requires creating means for full exchange of information and the opportunity for candid cross-critique. Certainly this last has occurred between the nutrition activities conducted by the several Institutes over which I have some uncertain sovereignty, and it has taken a healthy form. For example, NIH is a prolific producer of educational materials relative to nutrition. These are more designed to guide the professional than to educate the general public, certainly not to use a "hard sell," for reasons that I alluded to earlier—the lack of Federal intent in prior years to give authoritarian advice in an area of great economic sensitivities. Recent Congressional interest has given us an opportunity to read carefully some of our relevant publications. Some of them will be summarily retired: most will be revised. I also sense the probability of ecumenical publications arising from a resynthesis of once highly specialized information gathered by separate Institutes into a more useful whole, in coordination and cooperation with other agencies.



Thus, there is a need for maximum emphasis on resynthesis of this rich fold of nutritional information that we have been gaining throughout research activities across the whole field of biomedicine. There is an urgent demand in some segments of society, at this time, for a more "Keynesian"--cradle to grave--approach to nutrition.

We have two Institutes at NIH which aren't categorical and which ought to be engaged in a better clinical nutrition program than has been recognizable in the past. One of these is the National Institute of Child Health and Human Development, for whose maternal and child populations nutritional requirements are exquisitely important. This also happens to be the Institute that supports as much behavioral research as any agency in HEW. Questions are being asked about why people select certain nutrients, and how their choices can be affected. We need to pay more attention in our behavioral research to such questions and to devote more resources to it.

At the other end of the spectrum we have our newest component, the Institute on Aging. It has major responsibilities for attempting to enhance the value of life of that growing, graying sector of the American population. Here, too, there must be a clinical nutrition effort which will begin from the other end and move backwards toward that of Child Health and Human Development. At the same time, in every Institute we have disease-related research which has a high nutritional content and that, too, must be synthesized, as is possible and appropriate. It is for this reason that we have embarked upon a coordination effort of our own with the establishment of a trans-NIH committee on nutrition which has now been in existence for a year or so. It began with purpose and will steadily increase its power.



We do, then, have at NIH an instrument in place which forces the Institutes to consider, together, what their priorities should be and which has allowed us to get into some interdisciplinary interactions which I think are becoming increasingly important. At the present time, Dr. Seymour Perry is chairing the NIH Nutrition Coordinating Committee. So busy have been the activities of that Committee that, as of November 16, I also asked Dr. Artemis Simopoulos, whom all of you know from her previous position here in the Division of Medical Sciences, to be vice-chairman and executive secretary of that Committee. She is now devoting virtually all of her time to those activities. In the process of developing a biomedical nutrition research program at NIH, the Committee is organizing a national conference on "biomedical nutrition research in the 80s" to take place this summer.

I should remind you that the goals of nutrition research in this country, as carried out by NIH, are largely determined by the scientific community. That is to say, that by far the largest part of our nutritional program is carried out through the regular grant program and that the projects which are funded are largely based on peer review and on a determination of scientific excellence by our own peer review committees. It could be that there needs to be some interference with this "normal," traditional process. In some areas, targeting and determination of high program relevance already add coefficients to the market conditions set by peer review priorities. It is important for the nutritional community to marshall arguments for moving away from investigator-initiated research to emphasis on targeted or contract support, or even to center-concept funding, if indeed this both serves

more immediate national needs and enhances opportunity for discovery. NIH is prepared to listen carefully--and in the public interest, skeptically,--to such arguments.

I should like to close by answering the question of whether this town is too small for two big league teams in nutrition research. It has been raised at recent Congressional hearings and in social gatherings at the Old Executive Office Building. I am positive it isn't. We welcome the Agriculture Grant Program in nutrition and food sciences which is just being started. We at NIH have met with Dr. Key who is to head it. We have offered him all of the assistance we can as he develops the study section approach--the same kind of peer review that we have used. We want to encourage the healthiest and broadest interface that is possible between the Department of Agriculture and NIH in the field of nutrition research. I think that this kitchen is large enough to accommodate several cooks; a little increase in the heat means that more things are cooking and not that we are all about to explode.

TRANSCRIPT OF PROCEEDINGS  
OF THE  
DECEMBER 15-16, 1977,  
MEETING OF THE  
ADVISORY COMMITTEE TO THE DIRECTOR, NIH,  
ON THE  
PROPOSED REVISION OF THE  
NIH GUIDELINES ON RECOMBINANT DNA RESEARCH  
AT THE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND

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## CONTENTS

	<u>Page</u>
<u>Participants</u> . . . . .	5
<u>Opening Remarks by Dr. Fredrickson, December 15</u> . . . . .	6✓
<u>Introduction Section of the Proposed Revised Guidelines</u>	
History of the Revisions (Dr. John Littlefield) . . . . .	11
Definition of Recombinant Molecules (Drs. Littlefield & Singer) . . . . .	13
The Concept of Novel Recombinations (Drs. Fredrickson & Spizizen) . . . . .	15
Committee Discussion of the Introduction Section . . . . .	16
Invited Witnesses--Presentations and Discussion	
Dr. Ronald Cape . . . . .	18
Dr. Bernard Davis . . . . .	20
Ms. Nancy Pfund . . . . .	23
Mr. Leslie Dach . . . . .	28
Public Witnesses--Presentations and Discussion	
Dr. Arthur Schwartz . . . . .	31
Mr. Scott Thacher . . . . .	32
Ms. Francine Simring . . . . .	34
Dr. Jonathan King . . . . .	39
Dr. Wallace Rowe . . . . .	43
Dr. Mary-Dell Chilton . . . . .	46
Dr. Susan Wright . . . . .	48
Dr. David Gelfand . . . . .	51
<u>Physical Containment Section of the Proposed Revised Guidelines</u>	
Introduction to Physical Containment (Dr. Emmett Barkley) . . . . .	51
Committee Discussion of the Physical Containment Section . . . . .	56
Invited Witnesses--Presentations and Discussion	
Ms. Nancy Pfund . . . . .	61
Dr. David Gelfand . . . . .	63
Mr. Leslie Dach . . . . .	68
Public Witnesses--Presentations and Discussion	
Dr. Jonathan King . . . . .	64
Dr. Arthur Schwartz . . . . .	73
Ms. Francine Simring . . . . .	77
Dr. Bernard Davis . . . . .	79
<u>Biological Containment Section of the Proposed Guidelines</u>	
Introduction to Biological Containment (Dr. Susan Gottesman) . . . . .	80



## PROCEEDINGS

The meeting was called to order at 9:00 a.m., December 15, 1977, by Donald S. Fredrickson, M.D., Chairman, presiding.

DR. FREDRICKSON: Good morning ladies and gentlemen. We are very pleased to welcome you here today to seek your opinions and your advice on proposed revisions to the NIH Guidelines for Recombinant DNA Research. This is a special meeting of the Advisory Committee to the Director of the National Institutes of Health, and because we are going to talk about so many committees, this shall hereafter be known simply as "the Committee." This meeting is focused on a matter of considerable national and even international interest.

For this particular meeting the Committee's membership has been augmented to assure that its perspectives include sufficient expertise and opinion on relevant scientific, environmental, occupational, and many other public policy issues.

Current Committee members who are here today include Dr. James Neel, Dr. Jeanne Sinkford, and Dr. Katharine Sturgis. I should like to introduce them and other members who have specially joined us for this meeting. If I may proceed from my left, here is Professor James Gustafson, who is Professor of Theological Ethics at the University of Chicago; Dr. Katharine Sturgis, who is from Wynnewood, Pennsylvania; Dr. Roger DeRoos, Director of the Department of Environmental Health and Safety of the Boynton Health Service at the University of Minnesota in Minneapolis; and Professor Walter Rosenblith, Provost of the Massachusetts Institute of Technology. Next to him is Sir John Kendrew, the European Molecular Biology Laboratory representative. We especially welcome you from abroad, Professor Kendrew. Adjacent to Professor Kendrew is Ms. Patricia King, Associate Professor of Law at the Georgetown University Law Center; Dr. Robert Sinsheimer, Chancellor at the University of California in Santa Cruz; Dr. Ann Vidaver, who is from the Department of Plant Pathology at the University of Nebraska; Mr. Peter Hutt, returning for a second engagement, who is from the Covington & Burling Law Offices in Washington, who formerly was General Counsel of the Food and Drug Administration.

Dr. Karim Ahmed is from the Natural Resources Defense Council. Mr. Dennis Helms is Special Assistant to the Attorney General of New Jersey. Dr. Sinkford, who is not here at the moment--she is in court--is the Dean of Dentistry at Howard. We hope to see her later today. Next is Dr. Harold Ginsberg, who is Chairman of the Department of Microbiology at Columbia. Next, Dr. James Neel, Professor of Genetics at the University of Michigan in Ann Arbor. Then Mr. Jon Beaty, who is a student member of an institutional biohazards committee from Oregon State University. And next to him is Ms.--Where is Dr. Molina? I am sorry to have passed you. Dr. Mario Molina is from the Department of Chemistry at the University of California in Irvine.

Now, next to Mr. Beaty is Ms. Rosemary Menard, who is a laboratory technician and a member of an institutional biohazards committee at the University of Washington in Seattle.

Are there any that I did not introduce?

In addition to the members of the Committee who are seated about the table, I would like to introduce very briefly members of the NIH staff. Dr. Bernard Talbot, Dr. DeWitt Stetten, Dr. Charles McCarthy, Dr. Joseph Perpich, and Dr. William Gartland.

I should like to remind you that this meeting is being recorded throughout its proceedings.

We certainly welcome and appreciate your willingness, members of the Committee, to share with us the responsibilities inherent in an exercise like this. Apart from the expanded Advisory Committee, special arrangements for this meeting have also included the inviting of twelve witnesses to represent industrial research, academic research, and labor and environmental groups in scrutiny of the proposed revisions. In addition to these invited witnesses, a number of others have requested an opportunity to contribute their views on one or more aspects of the issues under discussion. Perhaps the latter are, in the purest sense, the public witnesses, whether they are scientists or represent other callings.

Present today are also members of two other groups that have had important roles in the development of Federal policy in this area. The Federal Interagency Committee on Recombinant DNA Research represents Federal departments and agencies that either support and conduct such research or have regulatory authorities that touch upon this activity. That committee also serves as a forum for discussion of recombinant DNA issues and for coordination of Federal activities.

I have also invited members of another Federal advisory board to which our society really owes a large debt of gratitude, and this group of experts is the Recombinant DNA Molecule Program Advisory Committee, or simply the Recombinant Advisory Committee, or RAC; and they have borne the burdens of interpretation of the Guidelines, and have labored for many months to prepare the proposed revisions that are the subject of this meeting.

Finally, we welcome several congressional staff members from committees that hold legislative and oversight hearings concerning recombinant DNA, and we also welcome members of the press.

A brief summary of relevant background might be in order at this point. NIH issued its Guidelines for Recombinant DNA Research in June 1976, and they were published in the Federal Register on July 7, 1976, for public comment. A draft Environmental Impact Statement on the Guidelines was released in September of 1976, and the final Environmental Impact Statement was released in November of this year.



The NIH Guidelines for Recombinant DNA Research were constructed painstakingly in response to insecurity that was generated by potentially powerful techniques for changing the genetic makeup of microorganisms. As you know, at the time the Guidelines were released, opinions about them ranged widely. Some, at one end, considered them barely sufficient, and others, at another extreme, found them so excessive as to possibly excite derision in future histories on American culture. And I think only one thing was accepted by all: that this is an area of science that is fundamental and rapidly moving, and that the Guidelines would require steady evolution in the light of accruing knowledge.

The Recombinant Advisory Committee has taken very seriously the task of modifying the rules to reflect an increasingly better understanding of this subject. NIH has taken equally seriously the duty to preserve due process and to provide for full public participation in this first major revision of the Guidelines. The RAC began early this year to frame revisions, and they were formally submitted to me last September 1. During that month they were then speedily published for comment in the Federal Register, and in the NIH Recombinant DNA Technical Bulletin.

Subsequently, the current Guidelines were compared with the proposed revisions. The comparison and the Committee's rationale for these are included in the Green Book, which I think all of you have been provided. In addition you have received an Orange Book in two volumes, which is a compilation of all letters received by the last week in December on the proposed revisions as published in the Technical Bulletin and in the Federal Register. Several additional letters have been provided to you as well. The members of the Committee have also received the final Environmental Impact Statement, published in November. That is the Yellow Book. And to complete the color code, you have received the International Report of the Federal Interagency Committee as the Blue Book. Additional copies of these materials are available in Conference Room 8, should anyone desire them.

Now, in the interim since the publication of the Guidelines, there have been some significant, major scientific events, and these will be referred to today, for they have given impetus to some of the proposed revisions.

A need for revision also derives from experience with implementing and administering the Guidelines. Approximately 110 institutions where NIH-supported research is going on have established institutional bio-hazards committees, and about 230 projects are now involved. NIH has established the Office of Recombinant DNA Activities, called ORDA, which is headed by Dr. Gartland, and has set up other means to deal with administrative requirements of the Guidelines, their interpretation, and the certification of host-vector systems. Development of both the central and the local administrative practices has taken time and resources. Imperfections in procedures and communications have been revealed, and the

section on roles and responsibilities needs strengthening. This will be discussed tomorrow morning.

As all of you are aware, there have been legislative developments in the past year on this subject. Upon the recommendations of the Federal Interagency Committee, Secretary Califano had legislation developed and an Administration bill was introduced into the Congress. Hearings were held on this bill and several others, but no legislation came out of the past session of the Congress. In the absence of legislation, all federally funded recombinant DNA research is being conducted under the NIH standards as currently agreed upon by all the agencies involved. In the private sector where work is not publicly funded, the pharmaceutical manufacturers, for example, have publicly given their assurance of voluntary compliance with the Guidelines.

Recombinant DNA research is also being conducted in many countries of the world. Many national and international bodies have reviewed this subject. The international aspects of the research have been analyzed in the report by the Interagency Committee--the Blue Book, to which I just referred. The report notes, for example, that the United Kingdom and Canada have also issued guidelines that differ somewhat in detail but are similar conceptually to those of NIH, and there are emerging other national versions of guidelines.

We are honored to have with us today a number of distinguished international participants in this discussion. I have already introduced Sir John Kendrew, who is serving on the Committee. At this time I would also like to introduce Dr. David Suzuki. Dr. Suzuki, were you able to make it? He was ill yesterday.

DR. MC CARTHY: We received a telegram that he is on his way.

DR. FREDRICKSON: Dr. Suzuki is a Professor of Genetics at the University of British Columbia, and the host of Science Magazine of the Canadian Broadcasting Corporation, and he has a long interest in this matter.

Other observers here include Dr. William Whelan, who is not from abroad, but from America, but who is Chairman of the Committee on Genetic Experimentation, so-called COGENE, which is a scientific committee of the International Council of Scientific Unions.

Dr. John Tooze--good morning. And Dr. Whelan is there too, with Dr. Tooze. Dr. Tooze is Executive Secretary of the Liaison Committee on Recombinant DNA of the European Science Foundation. Also we welcome Dr. Jan Zelinka. Good morning. Dr. Zelinka is the Director of the Institute of Molecular Biology in Bratislava, Czechoslovakia.

Recombinant DNA techniques and the policies governing their use can serve, for good or for bad, as a case model for public and scientific



COMMUNITY MENTAL HEALTH CENTERS AND  
BIOMEDICAL RESEARCH EXTENSION ACTS OF 1978

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HEARING  
BEFORE THE  
SUBCOMMITTEE ON  
HEALTH AND SCIENTIFIC RESEARCH  
OF THE  
COMMITTEE ON HUMAN RESOURCES  
UNITED STATES SENATE  
NINETY-FIFTH CONGRESS  
SECOND SESSION  
ON  
S. 2450  
TO EXTEND THE ASSISTANCE PROGRAMS FOR COMMUNITY  
MENTAL HEALTH CENTERS AND FOR BIOMEDICAL RE-  
SEARCH, AND FOR OTHER PURPOSES

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FEBRUARY 8, 1978



Printed for the use of the Committee on Human Resources

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WASHINGTON : 1978

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## CONTENTS

Text of: S. 2450.....	Page 4
-----------------------	-----------

### CHRONOLOGICAL LIST OF WITNESSES

WEDNESDAY, FEBRUARY 8, 1978

Richmond, Julius B., M.D., Assistant Secretary for Health and Surgeon General of the Public Health Service, Department of Health, Education, and Welfare, accompanied by Gerald L. Klerman, M.D., Administrator, Alcohol, Drug Abuse and Mental Health Administration; and Donald S. Fredrickson, M.D., Director, National Institutes of Health.....	10
--	----

### STATEMENTS

American College of Cardiology, Dean T. Mason, M.D., FACC, president, prepared statement.....	76
American College of Chest Physicians, Joseph C. Ross, M.D., FCCP, president, prepared statement.....	123
American Hospital Association, Leo J. Gehrig, M.D., senior vice president, prepared statement.....	39
American Library Association, Eileen D. Cooke, director, ALA Washington office, prepared statement.....	42
Association of American Medical Colleges, John F. Sherman, Ph.D., vice president, prepared statement.....	45
Association of Community Cancer Centers, John R. Nelson, president, prepared statement.....	48
Candlelighters, Grace Powers Monaco, representative, prepared statement.....	54
Cystic Fibrosis Foundation, Atlanta, Ga., prepared statement.....	65
Fox Chase Cancer Center, the, Timothy R. Talbot, Jr., M.D., president, prepared statement.....	74
Fredrickson, Dr. Donald S., Director, National Institutes of Health, prepared statement.....	35 ✓
Medical Library Association, prepared statement.....	84
National Association of State Mental Health Program Directors, prepared statement.....	98
National Council of Community Mental Health Centers, Inc., G. Kinsey Stewart, Ph.D., president, prepared statement.....	100
Regional Mental Health Complex, John R. Hutcherson, Ph. D., executive director, prepared statement.....	122
Richmond, Julius B., M.D., Assistant Secretary for Health and Surgeon General of the Public Health Service, Department of Health, Education, and Welfare, accompanied by Gerald L. Klerman, M.D., Administrator, Alcohol, Drug Abuse and Mental Health Administration; and Donald S. Fredrickson, M.D., Director, National Institutes of Health.....	10
Roswell Park Memorial Institute, Gerald P. Murphy, M.D., D. Sc., Institute director, prepared statement.....	129

(iii)

35

FOR RELEASE ON FEBRUARY 8, 1978

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20014

STATEMENT FOR THE RECORD

BY

DR. DONALD S. FREDRICKSON

DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ON

BIOMEDICAL RESEARCH AUTHORIZATION EXTENSIONS

BEFORE

THE SUBCOMMITTEE ON HEALTH AND SCIENTIFIC RESEARCH

COMMITTEE ON HUMAN RESOURCES

UNITED STATES SENATE

February 8, 1978



Mr. Chairman and Members of the Subcommittee:

Dr. Richmond has outlined for you the Department's proposals with regard to the four expiring NIH program authorizations, as well as certain amendments and new initiatives. I appreciate this opportunity to add a few observations and to elaborate on those proposals mentioned briefly in Dr. Richmond's statement.

Expiring Authorities

Dr. Richmond has summarized some of the more significant accomplishments of the National Cancer Program, the National Heart, Lung, and Blood Program, and the Medical Library Assistance Program. I will not repeat those here, but will provide more detailed descriptions of those programs, as well as a brief description of our research training effort, for the record.

With regard to the National Research Service Award (NRSA) program, we support your proposed amendments to the service payback requirement. As you know, the present formula provides that any recipient who fulfills part of the service requirement, but fails to satisfy it entirely, is penalized in that he or she is only given half credit for partial service. This arrangement is inherently inequitable and is serving to deter able people from entering into research training programs under NRSA auspices. We support an amendment to the formula that would provide proportional credit for partial completion of the service payback. Secondly, the Act presently recognizes that positions in research or teaching may not be available for all NRSA recipients and provides several other options for completion of the service

requirement. However, the present statute effectively discriminates against those who must choose certain options among those offered in that it imposes a requirement of 20 months for every 12 months of support in contrast with the requirement for teaching or research which amounts to 12 months for each 12 months of support. Again, we support a change to treat all recipients on an equal basis and require straight one-for-one payback regardless of the form of service.

A final concern about the research training program relates to the decline in applications for support of training in clinical research. Recent increases in salaries for interns and residents, coupled with the imposition of service payback requirements, appear to have diminished the attractiveness of research training programs for recent M.D. graduates. We do not know at this point if the problem is amenable to quick solutions through legislative or other means. However, I would appreciate your thoughtful consideration of how we might make clinical research a more attractive proposition.

Additional Amendments and Proposals for New Authorities

I would like to review for you the other proposals being submitted for your Committee's consideration:

1. Repeal of 20% arthritis set-aside. This amendment relates to the present provision in section 439(g) of the PHS Act, requiring that 20 percent of funds available for support of multi-purpose arthritis centers be made available each year for support of new centers. The effect of this requirement on the centers program is potentially very

destructive. The effect of a cumulative 20 percent earmark for new centers will be to preclude continued support of any established centers, and we urge repeal of this provision.

2. Distribution of chemicals and animals. The NIH currently has limited authority to make available certain research materials to investigators requiring them. For example, NIH may provide biological materials such as vaccines and standard reference materials for research involving biological products. We are proposing an amendment to section 301 of the PHS Act to permit NIH and other research agencies to make available standard reference chemicals and animal strains in instances where such materials are not commercially available or must be provided on a centralized, standardized basis. The budgetary impact of this amendment would be negligible and would be absorbed by the appropriate program. Provision of this authority would remove limitations that have proved troublesome for several NIH components, particularly the National Cancer Program.

3. Finally, Mr. Chairman, we are proposing repeal of an obscure and outdated provision of the PHS Act (section 321(a)) requiring the Surgeon General to furnish tobacco to patients in PHS facilities. This requirement--which is honored more in the breach than in the observance--is clearly inappropriate in view of our present knowledge about the effects of smoking on human health.

## ROLE OF THE FEDERAL GOVERNMENT \*

by

Donald S. Fredrickson, M.D. \*\*

Introduction

Mention of the office, let alone the functions, of the Director of NIH, can hardly be found in the statutes which authorize the formation of its many Bureaus, Institutes, and Divisions. Thus each incumbent Director may have his own views as to what are the important duties. To me, one of the most essential is that the Director keep himself at a neutral center, ever-objective, and utterly even-handed in views and reviews of all the 18 major components of NIH.

On this occasion I am aware that I am about to commit malfeasance. The NHLBI is too much in my heart and blood. Even my lungs are certain to reveal this sooner or later and I might as well admit my special weaknesses here and now.

After all, I joined the National Heart Institute in 1951, two years before I actually arrived in Bethesda. Before I had left the Institute 23 years later in 1974, I had tried on most of the hats--as a clinical associate, section and lab chief, as its first clinical director, third scientific director, and sixth director.

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\* On the occasion of the 30th Anniversary of the National Heart, Lung, and Blood Institute of the National Institutes of Health at the Washington Hilton Hotel, Washington, D.C.

\*\* Director, National Institutes of Health, Bethesda, Maryland 20014.



My life has been fashioned on its loom. The design shuttles back and forth, sometimes so tightly it suggests confusion. Once selected by Shannon to come here, I have twice succeeded him in two different posts. One still hears of the legendary power of Shannon to select people . . . a fact most often remarked upon by people who were selected by him . . . As much as any, Shannon shaped Heart--and was as much shaped by it. Given the wealth of leadership it has spilled out upon the rest of NIH, and American science, this institution has had a remarkable first 30 years.

I look out from my office window today upon the room where I had my first interview with Shannon--upon another window in that same building . . . the window of the room where I joined forces with other scientists in my first laboratory assignment. The other four were women (Thressa Stadtman, Marjorie Horning, Barbara Kalckar, and one other whose name I've forgotten.) It was several years before I realized that most scientists weren't women.

In order to provide for a balanced menu, you will note that there are three of us assigned to this portion of the program. It's a familiar triad: government, private, and industry. They are the reduction of human endeavor to fiducial elements. Yet the concept of a public-private partnership fostering good health is historically correct, economically essential, and practical.

- Federal

- relatively speaking, a newcomer to public-private partnership efforts in health and education and similar affairs
- now so dominant in sponsoring the scientific inquiry underlying changes in health practices.

- Private

- less in financial terms
- as much or more in essential flexibility of support
- industry - capitalization of developmental research
- paradoxically, too, the essential element in fulfillment of the opportunities created by new knowledge. The challenge of preventions has returned to personal and private behavior-- in such fundamental patterns as eating, smoking, and moving about.

What is this Federal role in all biomedical research?

Past--we all know what it has been

- History for 30 years;
- Division of Biomedical Research territory.

Present

- the fundamental support for a system of inquiry and the major determinant of the stability of the institutions in which the search goes on.
- Each year the government spends about 3.3 billion dollars to support R&D in the universities of America.
- One half of this comes from NIH.

Future--can it be less important--I do not see how--There is an increasing premium on knowledge. Each new increment is both an indicator of where more is to be found--and an imperative to find it.

It is really only the finite limits of the scientific method that sometimes raises bitterness against it. All the promises of the scientific rationalists in the Age of Enlightenment could never be kept. And we'd be at least another century in both explaining and apologizing for it.

What of the present and of the future of that piece of the biomedical research terrain under the curatorship of the National Heart, Lung, and Blood Institute?

This morning I had a special occasion to reflect upon these questions. I was at the side of the Surgeon General in a hearing room of the Senate. The subject was several NIH and ADAMHA authorizations. One of these was for the NHLBI. A routine renewal, one might think, for no-one argued against the proposition. Yet the dollar ceilings upon its appropriations under discussion were a sober reminder that the yesterday of exuberant growth of the research enterprise has given way to a frugal today, with its hard choices and forced selection among opportunities of seemingly equal promise. As we stand on the eve of appropriation hearings, these same hard choices are not unique to the field of cardiovascular research. It is a shared phenomenon--not only by many other enterprises--among which a Federal budget of finite size must be thoughtfully apportioned.

On several grounds this will be a year when, for research, in general the keynote will be "back to basics."

- President
- OMB directive to NIH
  - \$95 million  
from "applied" to "basic"
- NIH response--SAT
  - science base
  - applied
  - transfer
  - & training



- Response means more

to (R01)  
(P01)

What must give if resources remain at the same level?:

- (1) New applied starts
- (2) Transfer choices
- (3) Attention to center mechanisms

Other General Research Support to emphasize

- The
- investigator-initiated
  - autonomous
  - less differentiated research

These choices will be very difficult in the garden superintended  
by NHLBI

for • It is a relatively mature field, particularly in its  
cardiovascular acreage as opposed to its lung and  
blood divisions.

This means a potential harvest of useful applications several generations  
out from the rich science base from which they grew.

- clinical trials - an appropriate activity for an Institute,  
perhaps the only kind of research organization able to bring  
off such feats;

and NHLBI has led all the rest of NIH and the world in the  
mounting of giant randomized trials - the kind that I have on  
other occasions called the "indispensable ordeal."

- demonstrations
  - high-blood pressure -
  - the acid, practical test -
- It will impact on centers, too -
  - A proposed \$52 million for centers (of 3 kinds) in '78 . . . .
  - Few, if any new starts, this year.

- What is the longer range prospect?

I find it hard to project -

The success of cardiovascular medicine and surgery in the U.S. - and developed world - is phenomenal - and may have out-stripped organizational invention.

I have come to believe that the growth of centers for discovery can be inversely proportional to discovery itself. The great benefits of centers are more likely to lie in the important areas of applied research and technology transfer.

All in all, NHLBI this year exceeds the overall NIH Institute average in clinical applications and in transfer activities. Yet its portfolio of investigator-initiated grants is one of the largest in NIH. I have the priorities and ambitions and fears of all the Institutes now stored in my head for appropriations hearings.

My heaviest concerns in the cardiovascular area are for the purchasing power in the project grant line in the year to come.

Yet, we have all weathered more serious periods before. NHLBI is one of the blessings that a Director of NIH and the country can celebrate.

- Leadership within
- Citizen backing without
- One of the best organized planning and projection facilities with an excellent Council
- A brilliant cadre of scientists
  - its extramural grantees and contractors
  - its own intramural staff
- An absolute stunning record of achievement in scientific progress and practical progress
- A superb public sector in league with it - whose representatives you are about to hear.

We grew up in a time when cardiovascular diseases were seeking monopoly control of the human life span and well being. Aroused, the citizens formed an organization to fight it and Congress legislated a Federal solution. Both occurred in 1948.

Thirty years ago these gestures seemed typically American, like the creating of a public-private partnership against nature itself. It was an act of sheer hubris, of course, except that, by golly, it

worked. Death rates from heart and blood vessel disease are falling fast in America. A massive search for new knowledge and its extensive application have brought relief, cures, and most importantly prevention. For NIH and for America, the National Heart, Lung, and Blood Institute and the American Heart Association symbolize what people can do when they put their minds to it.



## OPENING REMARKS - BLACK HISTORY WEEK - February 13, 1978

Donald S. Fredrickson, M.D.  
Director, NIH

Once again, it is my great pleasure to welcome all of you to the annual observance of Black History Week at NIH and to kick off a truly outstanding series of programs.

It falls to me, as the occupant of the Director's chair at this great institution, to officiate at many scientific meetings, conferences and special events. I enjoy them, of course. But I get a special feeling of kinship at participating in the events that bring us together as a community of men and women. As you know, there are several that occur during the course of the year, such as the various ethnic weeks and cultural celebrations. But I believe none has the impact or the profound significance of Black History Week, and I take great pride in sharing it with you today.

Last year we were thrilled with the discovery of "Roots" the story of the Black American's proud heritage. A best seller as a book, Alex Haley's "Roots" became a television drama of extraordinary power and influence. For many people, it illuminated a harsh struggle and dispelled an ugly, stubborn myth.

This year we go beyond the rediscovery of the past. The theme of Black History Week for 1978 is Roots: Achievements and Projections of Black Americans. We'll focus on the

accomplishments of Black Americans in dozens of fields-- in science, literature, music, art, sports, religion, politics and statesmanship, among others. We'll highlight their contributions to society, but in an historical framework that will also highlight the obstacles they had to overcome. We will look at their aspirations, their hopes for the future.

And we will look at it in the context of a democratic society whose highest goal is the release of human potential and the growth of human dignity and independence.

We hope that this year's program will increase our knowledge of the past, deepen our understanding of the complexities of the present, and reaffirm our commitment to a future of continued growth and development of all members of the NIH family.

As I noted, we can look forward to an excellent line-up of programs this week.

We start off today with one of the outstanding local leaders in our country, the Honorable Maynard Jackson, Mayor of Atlanta, Georgia.

Mayor Jackson is the first Black mayor of Atlanta and the first Black Mayor of a major Southern city. Not only that, he is one of the youngest chief executives of a large

American city--now beginning his second four-year term at the of 39.

Mr. Jackson was born in 1938 in Dallas, Texas.

He entered Morehouse College in Atlanta as an early admissions scholar, and received his bachelor's degree there when he was 18. Mr. Jackson earned his law degree at North Carolina Central University, and thereafter became a principal in Georgia's first and largest Black law firm.

Though he is youthful by comparison to many of us, Mayor Jackson has already served a distinguished professional and public career.

It is a pleasure and honor for me to present Mayor Maynard Jackson -

Department of Health, Education and Welfare

National Institutes of Health

Statement by the Director

February 22, 1978

I am glad to have this opportunity to testify on behalf of the FY 1979 budget request for the National Institutes of Health. The Directors of the NIH Bureaus, Institutes and Divisions are here to discuss the programs for which they are responsible. I shall therefore confine this opening statement to a general overview of the budget request. Most particularly, I should like briefly to address the question of program balance and resource distribution that affects all of NIH.

Grants and contracts for extramural research, training, disease control, construction of research facilities, and assistance to medical libraries will absorb over 80% of the NIH funds requested this year. They will provide support for nearly two-thirds of all the non-industrial biomedical research done in this country. Preoccupation with the large, complex and varied extramural component of the NIH activities is therefore inevitable but I should like to emphasize that NIH is first and foremost a research institution--not only historically but in its day-to-day operations. Only 16% of the funds requested are for the intramural programs and other direct operations (excluding management) but 60% of the NIH staff



are engaged in the conduct of laboratory and clinical research and its ancillary supporting services and the largest share of the physical plant is devoted to this activity.

NIH scientists have made--and continue to make--significant contributions to the advancement of knowledge across the whole spectrum of the biomedical sciences. Moreover, they attract a large number of bright and highly motivated young people who, under their guidance and tutelage, are becoming first-class investigators in their own right. For 25 years NIH has been one of the world's most important research-training centers--especially suited for training young physicians interested in clinical research. The NIH in-house research effort is a major national--and, indeed, international--asset in the concerted effort to enhance man's capability for preventing, curing or ameliorating disease and disabilities. The American people can be proud of the dedicated men and women who make NIH the outstanding research institution that it is.

The prestige and respect accruing to NIH from its intramural research enhances the performance of NIH's extramural responsibilities, which include the husbanding of the nation's capability for expanding biomedical knowledge. This has always been apparent in the effectiveness of its peer review system, in the quality of administrators attracted to its Institutes and Divisions and highlighted recently by such ventures as the development of guidelines for research involving DNA and the orchestration of technology assessment as a continuous performance.

NIH is the world's largest single supporter of extramural biomedical research. One of our greatest concerns, which we know this Committee deeply shares, is the maintenance of a proper balance between various types

of research and research-related activities. Last month this Committee held an important and very useful hearing at which a group of eminent scientists stressed the need for maintaining a high level of support for so-called basic research. I say "so-called" because the phrase 'basic research' is without absolute definition and means different things to different people and at different times. Research is, essentially, an effort to gain new knowledge about something or to find a new way to use prior knowledge. Most scientists regard their efforts as 'basic,' no matter what the immediate purpose for seeking such knowledge may be. On the other hand, it could be said that all research supported by NIH is 'applied.' It seeks to apply the tools of physics, chemistry and other sciences to biology to the ends of bettering human health. When the National Science Foundation first started compiling statistics on Federal support for research, it included all NIH research funds under 'applied.' Since 1972 we have a computerized classification of research projects based on the output of different Study Sections to classify our research. We have launched several experiments in the past year and a half to test, confirm or improve the method. Reviews of the computerized classification of grants by executive secretaries of Study Sections, the initial review groups, by the Institutes to which the grants were assigned and by some of the principal investigators involved resulted in a great divergence of opinion. The experiments confirm the inescapable subjective nature of such a classification and have led us to a slightly different approach which can assist in an overview of the NIH operations.

Instead of the subjective classification of research into Basic, Applied or Developmental--a method whose acronym, BAD, seems appropriate--

it is more useful and more feasible to distinguish between the three principal aspects, or stages, of biomedical research on the basis of data we annually collect. We refer to this as the SATT system. With it we distinguish between

- ... The Search to expand and strengthen the Science-base for medicine and the other health-care disciplines, using as the model for that search the kinds of activities supported through grants for investigator-initiated research projects; the larger, multidisciplinary efforts (known as 'program-projects'); some center-based activities; and the provision of special resources for research. These activities are part of a continuum that shades into another, which as we define it, unequivocally represents
- ... Application and Development-of knowledge to inventions having immediate practical purpose. The data base for calculating this bloc includes the NIH clinical trials census and contract programs supporting other developmental research such as creation of special vaccines, other biologicals, drugs, instruments and other devices.
- ... Transfer-activities for the selection and dissemination of acceptable new technology to the health-care community--and, as appropriate, the public--including technological assessment and consensus activities, demonstration and control programs, and education; and, finally,
- ... Training of research manpower.

The extent to which Application and Transfer can be undertaken depends on the state-of-the-art and will thus vary widely from field to field, from Institute to Institute, and from time to time. In FY 1977, the last complete fiscal year, about three-quarters of all NIH funds were devoted to the Science-base search. Clinical application accounted for 15 to 20 percent of the funds, Transfer and Training each about 5 percent. Our next step in such an evaluation of resource deployment is aimed at a clearer view of how the Search base is differentiated in terms of diseases or objectives. For example, in our annual planning review we have this year looked at the distribution, across the whole of SATT, of resources for research in nutrition, prevention, diabetes and several other trans-NIH concerns.

The concerns expressed by the witnesses at the Committee's basic-research hearing were partly addressed to a feeling that funds for Search were being sacrificed to Application and Transfer. Some of their concern, specifically, was that funds available for investigator-initiated individual research projects were being eroded by disease-targeted programs. I share this concern over what is always a potential threat and, in some areas, a real danger. Investigator-initiated research projects--the traditional NIH research grants--provide an essential kind of support for much of biomedical research. They are directly responsive to scientific opportunities and draw upon the investigators' special energies to pursue their own ideas--judged to be good ideas by highly critical peers. This system of award allows flexible and rapid deployment of support according to opportunity and need to single out developing fields and to encourage innovative proposals which might be swamped by more orthodox and well-



established activities. This mechanism is also the entire route for drawing new scientists into research.

At the direction of the President, the FY 1979 budget request increases the allocation of funds to 'basic' research by 93 million-- from \$763 million in FY 1978 to \$856 million. In compliance with this directive, increases in the budget allowances for the various Institutes will be devoted primarily to Science-base activities, principally the support of investigator-initiated research projects. In addition, some funds from 'applied' or 'developmental' activities, principally contracts, will have to be reprogrammed to 'basic' research projects.

Application activities are well under way and must be continued and nurtured. There were nearly 800 clinical trials last year. A number of very large ones are still in progress, many started several years ago. The usefulness of such trials, which frequently involve the participation of physicians and hospitals in many parts of the country, depends on the adherence to of a common set of practices and uniform reporting of observations and results. The cooperation and degree of interest of the medical community in this effort was exemplified last October at an NIH conference on the methodology of clinical trials which had 700 participants, several hundred more than had been expected, all of whom paid their own way.

A major aspect of Technology-transfer, for which we at NIH feel a great responsibility, is the assessment of the validity, safety, and feasibility of the widespread application of new technologies. Last year we began what will be a continuing activity to examine numerous questions, having important medical dimensions, in ways that can provide the 'technical consensus,' or assessment of the state-of-the-art, needed by other agencies

of Government and society to make decisions on technologies involving questions of ethics, economics, planning, standard-setting or other social purposes. Consensus seeking exercises are not new to NIH—they have been going on quietly for many years—but in view of the momentum of research and our concern over possible adverse effects, these technology assessment exercises are being improved and redesigned to meet the need for more wisdom more quickly. An example was the consensus development meeting on breast cancer screening which we held at the Clinical Center last September. We now have an Associate Director for Medical Application of Research to coordinate these activities. Each of the Institutes will be scheduling consensus exercises for developments within its field that are potentially ready for further dissemination.

The NIH research-training programs are to a considerable extent shaped by the recommendations of the National Academy of Sciences. The budget request provides \$30 million for 2,053 individual National Research Service Awards of which 569 will be new awards. There is an increase of \$17 million to honor commitments to some 1,140 institutional awards but, except for the Minority Access to Research Career awards, no new institutional awards will be made. The total amount requested for training is \$147.9 million which represents an increase of \$16.9 million for the National Research Service Awards and a decrease of \$18.8 million for the old training programs which, after this year, will have been completely phased-out.

The overall increase in the budget request, over the comparable 1978 level, is \$42.3 million but, as there is a reduction of \$34.7 million in the amount for the construction of buildings and facilities, there is a

net effective increase of \$77 million. The budget includes \$27.7 million for the final phase of construction of the new Ambulatory Care Research Facility now under construction as an addition to the Clinical Center. The principal program increase is \$31 million for the population research and research for mothers and children, including the prevention of adolescent pregnancy, smoking and excessive drinking. I shall be glad, as will the Directors of the Institutes and Divisions concerned, to discuss these and the other modest program increases in the budget.

Department of Health, Education and Welfare

National Institutes of Health

Statement by the Director

March 2, 1978

I am glad to have this opportunity to testify on behalf of the FY 1979 budget request for the National Institutes of Health. The Directors of the NIH Bureaus, Institutes and Divisions are here to discuss the programs for which they are responsible. I shall therefore confine this opening statement to a general overview of the budget request. Most particularly, I should like briefly to address the question of program balance and resource distribution that affects all of NIH.

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The prestige and respect accruing to NIH from its intramural research enhances the performance of NIH's extramural responsibilities, which include the husbanding of the nation's capability for expanding biomedical knowledge. This has always been apparent in the effectiveness of its peer review system, in the quality of administrators attracted to its Institutes and Divisions and highlighted recently by such ventures as the development of guidelines for research involving DNA and the orchestration of technology assessment as a continuous performance.

NIH is the world's largest single supporter of extramural biomedical research. One of our greatest concerns, which we know this Committee deeply shares, is the maintenance of a proper balance between various types of research and research-related activities.

Last month this Committee met with a group of eminent scientists stressed the need for maintaining a high level of support for so-called basic research. I say "so-called" because the phrase 'basic research' is without absolute definition and means different things to different people and at different times. Research is, essentially, an effort to gain new knowledge about something or to find a new way to use prior knowledge. Most scientists regard their efforts as 'basic,' no matter what the immediate purpose for seeking such knowledge may be. On the other hand, it could be said that all research supported by NIH is 'applied.' It seeks to apply the tools of physics, chemistry and other sciences to biology to the ends of bettering human health. When the National Science Foundation first started compiling statistics on Federal support for research, it included all NIH research funds under 'applied.' Since 1972 we have used a computerized system based on the output of different Study Sections to classify research projects as 'basic' or 'applied.' We have launched several experiments in the past year and a half to test, confirm or improve the method. Reviews of the computerized classification of grants by executive secretaries of Study Sections, the initial review groups, by the Institutes to which the grants were assigned and by some of the principal investigators involved resulted in a great divergence of opinion. The experiments confirm the inescapable subjective nature of such a classification and have led us to a slightly different approach which can assist in an overview of the NIH operations.

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#### NIH INTRAMURAL RESEARCH

Dr. FREDRICKSON. We are glad to be before this committee again this year. I welcome the opportunity to present a general overview of the budget and you will have later opportunity to hear from the Directors of the various Institutes, Bureaus and Divisions. In my statement, I emphasized the importance of NIH to the support of biomedical research. Most of our funds go extramurally but I did put in a plug, as I think we should, for the highly important and well-functioning intramural program we have on campus. The prestige conferred on NIH by its intramural research also enhances our other functions such as the quality of the peer review system and the quality of administrators attracted to its Institutes and Divisions. This was highlighted recently by such ventures as the development of guidelines for research involving DNA and the orchestration of technology assessment as a continuous performance. Our ability to work out guidelines for research is certainly facilitated—if not actually dependent upon our ability to conduct research.

#### CLASSIFICATION OF RESEARCH

Last month this committee had an opportunity to meet with a group of distinguished scientists who were concerned with basic science. That followed, appropriately, almost a year and a half of activity at NIH in reviewing the distribution, or allocation, of resources and an attempt to create some better descriptors than basic, applied, and developmental for the range of our activities.

All definitions of the kind of research a researcher is doing are necessarily subjective and dependent on the point of view of the definer. We are taking cognizance of that, but we have, Mr. Chairman, examined this big terrain of biomedical research and we have attempted to use the data bases available to us to develop a better measure of activity from one end of the continuum to the other. At one end, where the state of knowledge is not very clear—and where research is therefore most needed—research is obviously not related to foreseeable practical application. It shades down to the cen-

Introductory Remarks

for

Dr. Eric Kandel\*

by

Donald S. Fredrickson, M.D.\*\*

Good evening, ladies and gentlemen, and welcome to the NIH lecture. Tonight's speaker is Dr. Eric Kandel of Columbia University's College of Physicians and Surgeons. Dr. Kandel's topic will be "Cellular Insights into Learning and Behavior."

Before hearing his remarks, however, it seems appropriate that we gain a few biographical insights into our distinguished speaker's own learning and behavior.

Dr. Kandel was born in Vienna and came to the U.S. at the age of ten. In 1952 he graduated cum laude from Harvard College, and in 1956 received his M.D. from New York University. Perhaps in deference to his Viennese heritage, Dr. Kandel's interests at this time centered on psychiatry, specifically psychoanalysis.

In 1957, Dr. Kandel came to the National Institute of Mental Health in Bethesda as a research associate. For the next three years, he investigated the cellular physiology of the hippocampus,

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\* Speaker for NIH Lecture held in Masur Auditorium, Clinical Center, National Institutes of Health, on March 29, 1978.

\*\* Director of the National Institutes of Health, Bethesda, MD.



that part of the mammalian brain which is believed to regulate memory. He found this investigation to be an exercise in fascination and frustration. The mammalian brain was far too complex in structure to yield the precise cellular and neural detail which was later to be his hallmark.

Nevertheless, Dr. Kandel's own hippocampus must have been in a highly receptive state when he came to NIH; because the first memories of doing basic research were apparently sweet enough to lure him away from the practice of psychiatry. When it came time to choose between the couch and the bench, so to speak, fortunately for us, he chose the bench.

Dr. Kandel, however, continued to maintain interest in psychiatry. After leaving the NIH, he did further research and teaching at Harvard and at the College de France in Paris as a PHS Special Fellow.

For the past ten years, Dr. Kandel has been professor of the Departments of Physiology and Psychiatry, first at New York University and, since 1974, at Columbia. During the same period, Dr. Kandel has headed the Departments of Neurobiology and Behavior, first at the Public Health Research Institute of New York, and, again since 1974, at Columbia University College of Physicians and Surgeons.

Over the past 20 years, Dr. Kandel has made many valuable and original contributions in the fields of neurophysiology and behavioral research. We are about to hear the fruits of his long

affair with Aplysia, the giant sea snail. Investigating this invertebrate's relatively simple nervous system, Dr. Kandel has begun to dissect and describe the neural circuitry or "wiring" which regulate specific behaviors and learned responses.

Let me close with this observation. B. F. Skinner and others of his psychological ilk are, like Dr. Kandel, also concerned with the study of behavior and learning. Within their behavioralist construct, however, investigation is centered upon input and output, stimulus and response. The nervous system or brain remains a "black box."

Dr. Kandel has begun to illuminate the processes of that black box. Behavior ceases to be the object of generalized observation, and becomes instead, the sequenced response of individual neurons. If we accept the notion that evolution has been very conservative, then many of the neural events that can be described in earlier, simpler nervous systems may be replicated or at least echoed in our own. Dr. Kandel has opened this door on the black box of behavior and, I believe, that his investigations are a paradigm for the future.

REMARKS  
before  
NATIONAL SCIENCE TEACHERS ASSOCIATION\*  
by  
Donald S. Fredrickson, M.D.\*\*

In January, a Harris Poll asked Americans to rank 20 major factors as to which will be the most important determinants of America's greatness in the next 25 years. The first place went to scientific research, a fairly easy winner over the runners-up: "industrial know-how" and "technological genius."

From one standpoint it's small wonder, really, that scientific research and its practical companions--technical/ industrial wizardry--obtained such flattering ratings. Take energy research, to pick one example. Everyone has at least a vague sense of the high stakes involved. Behind the laboratory experiments to promote atomic fusion is more than just the finding of another new use for lasers. If success should forever elude the scientists here, it could mean back to bearskins for all of us. But will there be any bears by then? As we face up to the inevitability of the end of petroleum fuels, and tussle with the difficult question of whether to make way in the neighborhood for a breeder reactor, we get a sense of how immediate is the need for some kinds of new knowledge.

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\*National convention of the National Science Teachers Association, Washington, D.C. April 9, 1978.

\*\*Director, National Institutes of Health, Bethesda, Maryland

In a comparison of the future with the past made in the Harris Poll, "hard work" slipped from second in importance, but only to fourth. This last should be reassuring to you teachers. Except that, on reading more closely, we discover the respondents were "adults" and not school children.

Why, we ask, couldn't Harris have polled the kids anyway? The 21st century will be more theirs than ours. Would they have responded the same way? I hope they would have found the central question of the poll a little chauvinistic. Is the "greatness of America" automatically synonymous with the "saneness of America" or with "a better world"? Most scientists work upon matters that may increase the knowledge of nature. The synthesis is a universal one. Contributions are accepted on the basis of their intrinsic worth and not according to the country of origin. Science will be harmed by any narrow nationalistic frame of reference.

Taking first place in the Harris Poll can't help but be reassuring to science. There have been recent signs of wear-and-tear in its relations with the rest of society. Science is basically a logical positivist affair and a reaffirmation of worth; any note of optimism will be welcome.

The relations of science and society since the beginning of its modern era in the 17th century have tended to be cyclical. Excessive enthusiasm, as in the Age of Enlightenment, has been



followed by periods of disillusionment, particularly as recognition is renewed that the scientific method is not applicable to the solution of all human problems.

Much uneasiness with the scientific method also derives from its products. The science and the technology tend to be confused, and dissatisfaction with the latter leads to ambivalence over the former. The late Jacques Monod put it rather dismally in Chance and Necessity.<sup>21</sup> Modern societies are woven together by science and living from its products, he says. And they have become as dependent on it as an addict on his drug.

Monod spoke this way because he was impatient that so many of these avid consumers persisted in clinging to other faiths rather than the fundamental ethic of science, i.e., "the systematic confronting of logic and experience is the sole source of real knowledge."

It is not clear that a majority of your recent graduates are ready to adopt so stark a confession, either. The revolutionary changes brought about through the physical and biological sciences in the last half century have been rather more than any two consecutive generations were prepared to absorb with peace.

The practical demonstration by the atomic physicists of the meaning of the Einstein equation was a dramatic shock. Now it is the biologists whose own pause for self-examination has

-4-

provoked much anxiety about the potential in new techniques for genetic recombination. (No free advertising this afternoon for recent, highly unscientific pretensions to new knowledge about human genetic engineering!)

The contrast of these modern discomforts with the great discoveries of the past is rather striking, however. Newton produced not a ripple in the British economy. No one was worried that Maxwell's "demon" was not kept locked in P-4 containment. Even the Copernican "heresies" went unprosecuted for a century.

It is sometimes said that the "public," meaning the average person, is not really concerned about the new powers of science, and that the challenges arise primarily from small groups of special interests which play skillfully upon the mercurial moods of Congress.

I have had a number of experiences in the past several years, however, which suggest otherwise.

- Breast cancer technical consensus.

The current guidelines for research with recombinant DNA are those promulgated by the National Institutes of Health. As its Director I have spent countless hours amidst this subject matter, which is of excruciating technical complexity.

I remember particularly the night that several colleagues and I sat about a conference telephone in Bethesda. From time to time there emerged the disembodied voice of a member of the Experimental Biology Advisory Committee of the City of Cambridge, Mass. To the questions of this group of concerned citizens, who I imagine were hovering over their telephone box, went back the best answers we could give. The subjects ranged from esoterica of molecular biology through practical details of the recently issued NIH guidelines. This complex subject has been treated to much theater, distortion in the press, and irrationality in debate. Our conversation with the citizens of Cambridge, however, clearly demonstrated to me that society, whose right to know is incontestable and whose need to understand is real, is intent upon achieving the essential communication between itself and science.

Living as we do in Washington, of course, it is possible to see first hand the developments in an important phenomenon. Sherwin wrote a particular useful summary of the thesis that an important response to the growth of science is the growth of government. This occurs (because) not only to protect the public interest as affected by new technology, but also "to foster further scientific advance." This last is crucial because the high cost of sophisticated and complex research requires that science stand in the queue for public support. In my own area, for example, nearly 30 percent of the support for the "basic

-6-

research" underpinning the health sciences is estimated to come from the budget of DHEW, most of it in the budget of NIH.

If government expands to control science and technology, it is important that people running government understand science and technology. Let me quote Chalmers Sherwin: <sup>31</sup>

"The revolution in science can be distinguished from the industrial revolution by the fact that a high school undergraduate can understand the principles of the latter. The steam engine, a railroad train, and, with a little more effort, even an electrical generator are within his grasp, but he gets lost in modern biochemistry, electronics, and nuclear physics. Mastery of this new knowledge is not quickly won. The subtleties of modern research and development, or even of technical production, are not easily learned late in life. But a manager must know the substance behind the problems he handles if he is to be effective. It is increasingly true that critical evaluation of substantive technical details is the very heart of policy decisions. The era of classical administrative formulation, 'You name it, I'll manage it,' is past."

A forecast of continuing trouble for three cultures--science, government and public. And, of course, C. P. Snow had the reasons years ago - "because our educational system is not geared to the source of our power." It would be very awkward for the rest of us



if the teachers could not be blamed for the greater social deficiencies.

I will not do so. It would be asking too much of me, however, not to presume a little upon the platform this Sunday afternoon has provided me. You will have perceived that, as teachers of science, you, too, are in an extraordinary position of influence and responsibilities in regard to a present dilemma.

Perhaps it was once presumed that your duties were limited to the attracting of the scientists-to-be, the fixing of them to their vocation by some irrevocable bond, and the sharpening of their talents for a lifetime pursuit of the unknown according to orthodox rules. It is true that you do have some important roles to play here, but I think that your major responsibilities lie elsewhere.

You will want ever to be alert to find and encourage unsuspected potential for science - minorities and women.

But more often, young homo scientificus will find you. He or she will already have gained or inherited some of the essentials:

- curiosity, discipline, drive.
- a perception of asymmetries and the compulsion to understand them.
- perhaps above all, a talent for metaphor in Aristotle's meaning of the word: the ability to

-8-

grasp the relationship between distant things.

How many of these qualities can you instill de novo through didactic method?

Whitehead talked and wrote of important stages of the education of one for science. He emphasized that early period of Romanticism,<sup>4/</sup> when the imagination must be aroused and curbs on the spirit were to be lifted. But this stimulating period will be partially over before you get your hands on the potential scientist. You will be engaging mainly in the second phase, laying on the discipline of logic, the rules and the compulsions for completeness of analysis and proof.

Several years ago I sat down to lunch with an African king. (Describe setting) He remarked that his people reserved their highest regard for their teachers and their doctors. "Who, Dr. Fredrickson," he said, "were the teachers who inspired you the most?" I had to pause; to be honest with myself. The images of two maiden ladies in black persisted.

- One was a tryant grammarian in the eighth grade, whose pince-nez oscillated furiously at the parsed sentences relentlessly upon the blackboard.
- The other was my old piano teacher--not so much for her pencil raps upon the sagging wrist or uncooperative fourth finger--but because she insisted one stick to the rules and data provided by the composer.

You will have some time with your proteges in Whitehead's third stage--that of the generalization of laws derived from data, and their proofs.

I urge you, above all, to also concentrate upon other virtues: humaneness and beauty in the period of Romance; ethics and morality in the period of rules and logic; and philosophy and metaphysics in the period of generalization. Prepare your scientist for tolerance of ambivalence and suspicion of science in his fellows. Failure to explain or communicate both method and interest has been a liability of science since its beginning.

You will be just one among many, then, who will shape the Young Scientist. You may be last, however, to have a critical influence on members of that far larger majority who will cope with the products, encourage the promises, and share the governance of science from without. How successfully you and your colleagues prepare these "outsiders"--the patrons of, and not the participants in, scientific research--will determine much of how well "America's greatness" is advanced by science tomorrow.

About 15 years ago, Donald Michael<sup>51</sup> wrote about policy making in Federal science that

"A cliché of our political folklore is that somehow the public will make everything right. In its wisdom it will judge between the contending power groups, evaluate technologies, establish a scale for priorities. But the

-10-

public, the third culture, hardly knows what is happening. .... It (The public) is caught between the (a publicity induced) fantasy world where science knows all the answers and a frustrating actuality ... caused ... in part by the inadequate or incorrect use of science and technology."

It must be your experience that most of the people in your science classes will not find their professional lives within the sciences. They have caught the romance. By the very choice of their electives, they also will have the intellectual gifts to acquire much of the necessary discipline:

- an understanding of the scientific method;
- an historical perspective of where science has contributed and where it has failed in solving human problems;
- a proper degree of skepticism, and at least some talent for inductive analysis.

It is from the ranks of these--your other pupils--that likely will come those specimens of homo publicus who will most effectively intervene in the confrontations we have described and anticipate. They will self-select away from science as a profession for numerous reasons. But you can be cheerful--not mournful--about these losses, if you have strengthened their capacity to promote and to govern wisely the power of science--



and to translate to their fellow citizens the heightened perspectives they have of the promised lands.

There are even more important encounters of the third kind. Ones that I fear you may all not be seeking enough.

Recent trends have suggested that the average citizen has sensed some limits to the doctrine of parens patriae - the old doctrine in Anglo-saxon law -- ..... guardianship of government.

- Laetrile
- Saccharine

The citizens must retain those discretionary powers. They will -- but the obligation remains to be able to read a label.

Other matters of health have become affairs of state -

- smoking
- diet
  - content of: calories
  - cholesterol
  - junk
- other aspects of prevention.
- conservation

are responsible for

Six percent of people/40 percent of the  
annual withdrawal of resources from the only  
planet we have.

Scientific research has only a certain minimum value to any civilization which cannot wisely convert the information and knowledge provided into folk wisdom.

-12-

Your third task is the most difficult - to reach those who shun the classes you teach.

This educational disjunction is not of recent origin. It has always placed a limit of one kind on the speed with which any culture adapts to its inventions. As the products of science and technology accumulate higher, however, we wonder if there ever has been enough, or is now enough invention in education itself - to cope with the demand for assimilation.

#### CODA

Have you read the deeper message in the Harris Poll? Superficially, it says that Americans believe that scientific research is the prime determinant of the future. Obviously, this means not only promotion of good science and care to see that the processes of inquiry and of discovery are not injured by excesses in external regulation or ultimate expectations. It also implies the prudent and humane use of all the products of science.

These are general tasks, not left to a small professional elite. Their performance depends upon the general level of understanding of the subject.

It is, my friends, you, the teachers of science, upon whom has fallen the principal trust for America's greatness--perhaps even the survival of our kind.

## FOOTNOTES:

1. The Washington Post, January 16, 1978
2. Jacques Monod, "Chance and Necessity"
3. Chalmers Sherwin, "Science, Public Policy and the Scientist Administrator; An Anthology," National Institutes of Health, Public Health Service, USDHEW, Bethesda, Maryland 1970
4. Alfred North Whitehead, "The Aims of Education," The New American Library of World Literature, New York, 1955.
5. Donald Michael, "Science, Public Policy and the Scientist Administrator; An Anthology," National Institutes of Health, Public Health Service, USDHEW, Bethesda, Maryland 1970

E. LEONG WAY, PRESIDENT



EUGENE L. HESS, EXECUTIVE DIRECTOR

# NEWSLETTER

Office of Public Affairs — Walter J. Ellis, Director  
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American Association of Immunologists

Volume 11, Number 5

May 1978

## SPECIAL EDITION

"THE ADMINISTRATION'S VIEW OF BASIC RESEARCH AND THE LIFE SCIENCES"

FOR THE BENEFIT OF THOSE WHO WERE NOT AMONG THE 1,200 ATTENDING THE PUBLIC AFFAIRS SYMPOSIUM APRIL 10 AT THE FASEB ANNUAL MEETING IN ATLANTIC CITY, THIS SPECIAL EDITION OF THE NEWSLETTER PRESENTS TRANSCRIPTIONS OF PRESENTATIONS AND RESPONSES TO QUESTIONS BY:

- DR. GILBERT S. OMENN  
ASSISTANT DIRECTOR, WHITE HOUSE OFFICE OF  
SCIENCE AND TECHNOLOGY POLICY
- DR. DONALD KENNEDY  
COMMISSIONER, FOOD AND DRUG ADMINISTRATION
- DR. DONALD S. FREDRICKSON  
DIRECTOR, NATIONAL INSTITUTES OF HEALTH ✓

THE SYMPOSIUM WAS PLANNED BY THE FASEB PUBLIC AFFAIRS COMMITTEE, DR. LOWELL M. GREENBAUM, CHAIRMAN. DR. GEORGE K. DAVIS WAS MODERATOR FOR THE SESSION. TRANSCRIPTIONS BEGIN ON PAGE 2.





REMARKS AND RESPONSES TO QUESTIONS OF  
 DR. DONALD S. FREDRICKSON, DIRECTOR  
 NATIONAL INSTITUTES OF HEALTH  
 FASEB PUBLIC AFFAIRS SYMPOSIUM  
 ANNUAL MEETING, ATLANTIC CITY, APRIL 10, 1978

It's a pleasure to have this opportunity again this year. So much of our lives are intertwined, yours and ours at NIH. One of the best benefits we can derive from this meeting is to make sure you have ample opportunity to say what's really on your mind, anonymously if you like. And thus my plan this evening is to take up two or three topics very briefly in outline, and stop between them and see if you would like to ask some questions about them.

My two colleagues and good friends who have preceded me have already brought up a number of things, and so have you in questioning. Perhaps one way for me to start is to mention a topic which I think is pertinent and important--that relating to the boundaries of NIH--what is it supposed to be doing and what is it going to do about basic research? In this connection, we might look at the last FASEB Newsletter, which some of you have seen, and turn to the article titled "NIH Liberation Act?" [About the Kennedy bill to create the National Institutes of Health Care Research]

Every morning as I come to work I go by Jim Shannon's picture and I say, "Jim, the place is really still the same. It is the world that is different." The world is a lot different, but I realize that NIH has changed since the time that he retired in 1968. We then went into a period of stable--or maintenance of--purchasing power jolted by some extraordinary special mandates which reached the end of their fuses. And then we entered the current period of very narrow mandates. It may be that this President, abetted by the able Science Adviser and his colleague, Dr. Omenn, may have made another turn in the road, one of great significance in regard to our own agency as well as all the R&D support from the Federal Government.

National Institutes of Health Care Research

But let me return to the boundary question. Not long ago Senator Kennedy introduced a bill to create another set of National Institutes of Health, this time the National Institutes of Health Care Research. It is designed to create a new home for the National Center for Health Statistics, the National Center for Health Services Research, and to create another Institute, one for a Center for the Evaluation of Medical Technologies. It will do a number of things in the area of technology transfer and attempt to upgrade a capability which is extremely important because of the current agonies of the country with respect to cost containment.

After listening to Dr. Kennedy and to Gil Omenn, I realize the problems that basic science has in this still affluent Nation result primarily from the urgency of the problems that eventually they are going to resolve, and because of the expense and the clumsiness of the partial technologies that are all we have at the moment to solve these problems. What we see is the conjunction of two forces: the tradition of inquiry of extraordinary capability, attempting to go more or less on its same course and about to collide with some of the other problems which seem to be of now unavoidable immediacy.

And so it is with the proposed National Institutes for Health Care Research. They too would deal with some problems I think are real, and that NIH is not covering at the present time--and some which I think it should not. But keep in mind, of course, that the creation of a seventh Public Health Service agency inevitably can only bid for what is now a melting pot of new monies in each Federal budget, and that thus this introduces only a possible new solution to some of these problems which will have to be paid for from the funds that are available for the other activities which have heretofore seemed so much more important. And this is a way of life as we try to meld the process of and lasting capacity for scientific inquiry and discovery with the real time problems that the public also wants to solve.

#### Defining the NIH Mission

The NIH has made some headway this year in trying to further define its boundaries. One has to be very selective, but we have begun to feel that some of the arguments for what NIH must not do and what it must do are beginning to receive some approbation, both in the Administration and the Congress.

Without question we have the need to engage the immediate as well as the distant goals. Science cannot step back one pace from its social responsibility to help evaluate the new inventions that it would bring to bear upon the human condition.

The idea that NIH might foster a broad continuum of research and medicine has been recognized from the beginning as having great virtue. This has included a recognition that the whole process is continuous; that it was most efficient to carry it out in this way; that it was essential that certain kinds of hybrid expertise would be required for the gradual translation of new biology knowledge, new fundamentals into practical invention that would help heal the sick and certainly eventually prevent their diseases. And I think that idea still has extraordinary merit. Thus I face with some trepidation the question of where the life must be drawn at the boundaries of where NIH should be responsible and where it must stop. I must say that, in fact, one of the most difficult parts of that job is the fact that in the PHS we still don't have adequate complementarity of the other agencies that are allied with NIH in the march for development of new knowledge and its application for prevention and for regulation and, particularly, for care.

Although some have been terribly concerned that we might not, I think we have managed thus far to avoid increasing seriously the degree to which we have engaged in activities that most believe NIH should not have as part of its mandate. One of these is regulation; another is long-term health care commitment.

But there is also a third area in which I think we have to be particularly careful that we engage with the utmost trepidation. This is where we get too heavily involved in promotion. For example, one of the success stories of the NIH and one of its fine Institutes, The National Heart, Lung, and Blood Institute, is its successful catalysis of the promotion of its campaign to find people with high blood pressure and to get them under treatment. This is a well-targeted and well-organized campaign, and it has shown some extraordinary success. With six million dollars of NIH money, it has attracted some \$50 million of outside government money and private money into this campaign. At the same time the Institute is conducting a long-range clinical trial to prove that the detection and treatment of hypertension is actually worthwhile. The irony of this is not quite so great as it may appear, because a major objective of the Institute today is to find those diastolics over 105, and a major but not sole objective of a second trial is to work at those with even lower blood pressure. But it does illustrate the question of what could happen to an agency whose objectivity must not be compromised, when it is also

committed to promotional activities were there to become a national need for some re-evaluation of an already established program.

Let me be more specific. There still are 50% of the water resources in this country that are not fluoridated. Many of these represent areas where there will never be fluoridation for technical reasons and, in others, where there still is uncompromising opposition to this technique. Our National Institute of Dental Research contains almost 100% of the expertise within the Federal Government for dealing with this problem, and it might readily engage in a very intensive fluoridation program. But the question then comes to our mind: Suppose that it were to be discovered in Transylvania that fluoridation were to cause infertility? To whom would we turn in this country for an objective answer?

Thus in those control activities which are very popular with the Congress and which are now conducted by several Institutes, we are trying to make sure that we not get so deeply into efforts to control disease that we are involved in regulation or in continuing delivery of some forms of health care. We try to retain the objectivity of the research Institute so that its principal mission is not compromised. We believe the appropriate definition of control activities for the NIH should be retained for demonstrations in which there is still an element of a scientific question to be solved. At the same time, we must try to build up the strength of certain other agencies whose mission is more clearly preventive promotion so that they can carry on the task with the essential knowledge when it becomes available.

#### New Funding Strategies

Now, finally, we are beginning to gain acceptance within NIH and within the Administration, and slowly within the Congress for a new set of institutional funding strategies which bear very heavily on the question of basic science support.

Fortunately for more than a year we have been hoping and anticipating that the Administration might come through with a strong call for strengthening of some of our resources for basic research. The only problem was that we didn't know how to define basic research. The algorithm that NIH used had been constructed by the arbitrary assignment of the output of one set of Study Sections to basic research and of another set of Study Sections to applied. If we were to cut a swath across this room, you would find that some of you who believe you are on heavily basic research would actually have been doing applied by this definition, and it would be your support that would be waning and the support of colleagues to your right and to your left which would be increasing.

As we worked on this question through the year, we found that we had several data bases that could be used to cut NIH activities into four parts, which would be useful for purposes that are so important to us in regard to the new initiative of the Administration to emphasize basic research.

For one thing we have now a very extensive index of clinical applications work--clinical trials. NIH now has about 200 million dollars in this kind of activity, as well as certain contracts for the development of new drugs and for other activities that are very clearly developmental, carrying biological ideas along to practical use. All of our clinical trials and developmental contracts have been placed in our "A" (for applied) category.

There is an additional relatively small amount of activity which is related to technology transfer. This encompasses the demonstration and the control and the educational activities which I think are important provided they are carried out within the boundaries that resemble



those I discussed. This category we designate with a "T" (for transfer).

Thirdly, there is the area of research training, also designated with a "T."

And, finally, that which is left we have called "S" for science base, because these are the activities which are primarily investigator-initiated research which, after all, goes to expansion of the science base. On this SATT system, then, we are going to construct the projections that will attempt to accommodate the new initiative of the President to turn nearly 95 million dollars more of our budget into the lines which represents our "S" (or science base list of activities), that is, into the R01s and P01 grants.\*

At this time NIH has about 800 million dollars in R01s. The purchasing power in that line has remained about the same in constant dollars for the last ten years. One of the most striking increases in this line will occur as the National Cancer Institute undergoes an intensive reorganization during this year where a large fraction of its now contract-based research will be thrown back into the support of R01s and be awarded through the peer review system.

There remain many aspects of this analysis to be further refined because alongside program projects and R01s there are several other funding mechanisms, many of them having to do with centers. And thus one of our tasks this year is to see if we can further focus on just what it is that would be required to maintain the capacity for increasing the science base in an appropriately vigorous and vital fashion in this country. Because I think that ultimately, perhaps not too long from now, one of the solutions to part of our problem may be that we ought to try to convince the Congress to give us an authorization of "S" (for science base) and that we develop along with the scientific community some kind of reasonable definition of stable support that might be guaranteed through the appropriations process for five or more years.

Such a guarantee even if only keeping up with inflation would permit us to predict with complete assurance that we could at least maintain a stable system. We could also devise within it ways to award money to individuals and to groups of scientists and to institutions in a fashion that would provide greater flexibility and more certainty of support for those engaged in this system. And so we are attempting to break out better definitions with this stable system in mind. Once one could assure the science base on a longer term, then it would be far more appropriate for each Institute and the Congress themselves to engage in lengthy debates about what new money should be applied for what new great initiatives, for clinical trials, for development of vaccine and drugs, or other uses for the knowledge which would continue to pour from the science base.

Well, that's all I want to say about that for a moment and I will open up the floor for a few questions about R01s, funding, or any questions you might have in that particular line.

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\*R01 is the NIH designation for research project grants, which generally are initiated and conducted by a single investigator. P01 is the designation given program project (multiproject) grants which support a group of investigators working on a related set of problems.

# RECOMBINANT DNA ACT

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HEARING  
BEFORE THE  
SUBCOMMITTEE ON  
SCIENCE, RESEARCH AND TECHNOLOGY  
OF THE  
COMMITTEE ON  
SCIENCE AND TECHNOLOGY  
U.S. HOUSE OF REPRESENTATIVES  
NINETY-FIFTH CONGRESS  
SECOND SESSION

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APRIL 11, 1978

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(II)

## CONTENTS

### WITNESSES

	Page
April 11, 1978:	
Dr. Philip Handler, president, National Academy of Sciences-----	4
A. R. Whale, assistant secretary and general patent counsel, Eli Lilly & Co.-----	94
Dr. Robert A. Alberty, dean of science and professor of chemistry, Massachusetts Institute of Technology-----	103
Ms. Pamela Lippe, assistant legislative director, Friends of the Earth, Inc-----	104
Dr. Gil Omenn, Assistant Director for Human Resources, and Social and Economic Services, Office of Science and Technology Policy----	135
Dr. Donald Fredrickson, director, National Institutes of Health; accompanied by Dr. Louis La Motte, director of Licensure and Proficiency Testing, Bureau of Laboratories, center for disease control, and Dr. Robert Elder, Deputy Associate Commissioner of science, Food and Drug Administration-----	161 ✓
Appendix—Additional material submitted for the Record:	
Philip L. Bereano, associate professor, University of Washington, Seattle, Wash-----	179

Mr. BROWN. You may proceed, Doctor, as you see fit.

STATEMENT OF DR. DONALD FREDRICKSON, DIRECTOR, NATIONAL  
INSTITUTES OF HEALTH, ACCOMPANIED BY DR. LOUIS LAMOTTE,  
DIRECTOR, DIVISION OF LICENSURE AND PROFICIENCY TESTING,  
BUREAU OF LABORATORIES, CENTER FOR DISEASE CONTROL,  
AND DR. ROBERT ELDER, DEPUTY ASSOCIATE COMMISSIONER OF  
SCIENCE, FOOD AND DRUG ADMINISTRATION

Dr. FREDRICKSON. Thank you, Mr. Chairman, we are very pleased to appear before the subcommittee today to testify with respect to H.R. 11192, the Recombinant DNA Act. I have a statement that has been placed in the record. I will read certain portions of it that should be highlighted.

The Department favors enactment of this legislation, Mr. Chairman, because the measure offers the most promising solution available for establishing national standards for the use of recombinant DNA techniques. I should like to echo the laudatory comments of the previous witness with regard to the activities and hearings of the subcommittee on recombinant DNA issues.

It is a matter of public record that the field is moving rapidly, and it is necessary to adopt measures that are sufficiently flexible to allow us to apply common standards and yet keep up with the movement within the field itself.

I support the principle of flexibility, particularly the exemption aspect as contained in 11192. I think it is extremely important that there be an opportunity to exempt, after careful consideration, certain experiments from the guidelines. This is for several purposes: One, to provide the opportunity to do certain risk assessment experiments; two, to eliminate any excessive regulatory burden imposed by experiments that have been clearly shown to clearly pose no significant risk to health or the environment.

Over the past 1½ years, the implementation of the guidelines has proceeded reasonably well. Some experiments have had to be postponed and some scientific work delayed by the presence of the guidelines and by their implementation. Still the spirit of cooperation between NIH and the local institutions has remained good.

The NIH has reviewed actions by institutional biohazards committees to insure that research protocols comply with the requirements of the NIH guidelines.

We note that in the Commerce Committee's bill report accompanying H.R. 11192 the general administrative structure of the guidelines is endorsed for purposes of regulation under H.R. 11192.

Indeed, it is important that the Commerce Committee report encourages the Secretary to place most of the authority for local administration of the act in the institutional biohazard committee. We are considering in the proposed revisions of the guidelines further responsibilities for these biohazard committees.

In our view, it is essential that the responsibility for primary oversight lie with these committees rather than centrally in Washington, D.C.

These local institutional responsibilities must be increased in view of the impossibility of any sufficient Federal police force to enforce standards externally. And, indeed, a corollary of this is the need for a common set of Federal standards.

This was the belief of the Interagency Committee on Recombinant DNA Research that recommended preemption to insure a single set of national standards in its March 1977 report. We strongly favor preemption.

It is the administration's view that a standard of reasonableness, as determined by the Secretary, rather than necessity as in H.R. 11192 should apply when State or local governments petition to have their requirements govern. I would like to point out, Mr. Chairman, that the NIH guidelines provide for strict standards to govern this research, and in no sense should they be considered minimum national standards. State and local governments will recognize the prudence and the conservatism of these standards and find them to be a high standard for the protection of health and the local environment.

We have encouraged public participation at the national level. We met in December to consider proposed revisions for the present guidelines. At the local level we have made recommendation for diverse membership on the institutional biohazard committees. These recommendations are included in the present guidelines. We are considering further mandates for public representation on these committees as they assume increased responsibilities for monitoring and oversight.

The present revision of the guidelines, not yet final, proposes that there be not fewer than five members on such committees. They must have adequate scientific expertise to make decisions and in some cases there must be on that committee a biological safety officer that meets certain requirements of background and training.

We also believe that there must be at least one, and maybe several, public members who have no ties to the institution and no financial interest in its activities.

I would certainly say that we believe that the expertise of the committee to interpret the guidelines is an important, although not the sole, requirement.

It will be very probable that, as with our experience with the review committees that review human experimentation, people who do the kind of work being examined must be among the members of the committee in order to provide the necessary expertise.

It is quite possible and necessary to avoid issues of conflict of interest; for instance, to assure that when a committee member's own project is being considered that he or she be removed from those deliberations.

We will urge, as we have in the past, that meetings be open to the public and indeed it is our experience most of them are in such institutions. But this decision is the institution's.

Whether open or closed, we require that the minutes of the meeting be available to the public.

We are considering the possibility that for some institutions it may be necessary to create area, rather than institutional committees, because the necessary expertise might not be available in that institution.

We have recently issued a decision that recombinant DNA research



inventions developed under DHEW support may be patented by universities provided the licensees adhere to the safety standards of NIH guidelines.

We are currently also considering inserting in the revised guidelines provisions that will provide protection for proprietary and patent information, but that will not compromise public disclosure of information on potential risks to the health or environment. The Commerce Committee report specifically states that the Department should include in regulations implementing this act provisions for the protection of proprietary data.

NIH filed an environmental impact statement (EIS) on the recombinant DNA guidelines in October 1977 and in relationship to the current revisions we are conducting an assessment of their environmental impact, if any.

As you know, the National Environmental Policy Act requires an EIS for "major Federal actions significantly affecting the quality of the human environment." It should be noted that in the Commerce Committee's report it is stated, and I quote, "It is the committee's understanding that the Secretary will complete and file an EIS on all guidelines and regulations, as expeditiously as practicable, even after promulgation of the administrative regulations . . ."

Under NEPA's requirement it is more precise to say that the Department will conduct an assessment of the possible environmental impact of the standards and regulations. And based on the assessment document a determination will be made on whether an EIS is required.

Presently, we are moving to develop a decision document and an environmental impact assessment of the proposed revisions in order to put them into effect as rapidly as possible—but only as rapidly as is in accordance with the Administrative Procedures Act—so we can avoid unnecessarily heavy regulatory burdens—such as those in the current guidelines.

My final comment is that it is clear that regulatory responsibility will need to be further defined in the event of the passage of this act. When testifying before the Subcommittee on Health and Scientific Research of the Senate Human Resources Committee, April 6, 1977, Secretary Califano said, "NIH [will] recommend the revisions in the guidelines, review, and clarify the technical issues, and handle, if you will, the standard setting, the philosophy, the scientific input, and then turn over to CDC the functions of licensing facilities and maintaining the registry and operating and promulgating standards. Both organizations would obviously have to be involved in training workers and in working with those outside the Federal Establishment as well as inside that are involved in recombinant DNA research."

Indeed for the past 18 months, NIH has worked closely with the Center for Disease Control (CDC) concerning safety aspects of the guidelines.

For example, the two agencies have been developing mechanisms for assisting institutions in managing laboratory emergencies and for providing direct assistance when appropriate.

Also, NIH and CDC have been reviewing packaging and shipping requirements relevant to these activities.

Further, the two agencies have collaborated closely in revising the CDC Classification of Etiologic Agents on the Basis of Hazard. This

classification scheme underpins some of the safety requirements of the guidelines.

Close coordination and consultation with the Food and Drug Administration and the Environmental Protection Agency will be essential since these agencies' regulatory authorities will come into play when recombinant DNA technology is ready for commercial development.

OSHA will continue to exercise its regulatory authority in the workplace.

In conclusion, the subcommittee is to be commended for its enormous efforts to educate the public and the scientific community in these matters.

I would like to thank the members of the subcommittee for the continuing interest in the development of these recombinant DNA policies.

Mr. BROWN. Thank you very much, Dr. Frederickson.

Do either of your colleagues wish to make a statement at this time.

Dr. FREDRICKSON. I would like Dr. Elder to make a statement in reference to a point he observed in the report.

Mr. BROWN. Could we ask him to correct any errors you made in your statement?

Dr. ELDER. Thank you very much. But I will decline that opportunity by referring back to Dr. Frederickson's testimony.

He noted the intention of providing guides for the biosafety committees at the local level. I think it is important we clarify that the guidelines are applicable both to the institutions and to individual companies.

In the Commerce Committee report there are problems in the interpretation as to how section 105(e) of the bill would be applied to industry versus an institution such as a university under the conflict of interest section. It might present a problem if handled in a different manner, as one might conclude from the earlier committee report. We prefer the institutional approach for all local biosafety committees.

Mr. BROWN. Thank you.

Mr. FUQUA. On the preemption provisions, do you see this as an important feature, the way that the bill is outlined?

Dr. FREDRICKSON. I think preemption is an extremely important feature—or an essential feature, in my view, of this bill.

As I commented, during the portions of my statement that I read, it is the administration's feeling that the adjective necessary or the test of necessity could be sacrificed and one of reasonableness will be adequate.

Mr. FUQUA. Is that your position?

Dr. FREDRICKSON. Yes; I accept that as an adequate provision for the preemption of State or local regulation as long as it is clear that it is the Secretary who determines what is or is not reasonable.

Mr. FUQUA. Thank you.

Now, under the new guidelines that NIH has been formulating, in these do you see overly restrictive language for the researcher?

Dr. FREDRICKSON. Certainly our whole striving during this process of revision, which is a very lengthy and involved one, is to come to a point where we can honestly believe that we have not unduly restricted scientific activities, and at the same time retained the necessary protection of the public interest in this still uncertain and unfolding area of research.

Mr. FUQUA. Do you still feel this is an uncertain type of research?

Dr. FREDRICKSON. Most certainly it is. Although I think we are constantly learning, I think it is fair to note for the record that throughout the period that we have experienced the development and promulgation of the guidelines and considering their revision through multiple public hearings and a deluge of correspondence and conversations that it is important to know that not a scintilla of evidence has been presented or developed of any of the horrors that have been envisioned or considered possible under the use of recombinant DNA techniques. There is no evidence that any of these have materialized even though there has been continuing use of these techniques.

Mr. FUQUA. I am glad you mentioned that because I think it's very significant that the scientific community in this area has been most honest and forthright, in their concerns about this.

Dr. FREDRICKSON. Yes; thank you.

Mr. FUQUA. Also at the same time there has not been any cause for alarm as a result of any of the work that was done. I think that is a compliment to the scientific community and to the researchers that have been working in this particular field.

Thank you, Mr. Chairman.

Mr. BROWN. Go ahead, Mr. Thornton.

Mr. THORNTON. Thank you.

Now, in light of your last statement, there is no evidence of any actual hazards having been determined by experience that had existed. I wonder whether the purpose of legislation might be accomplished by continuing in effect the guidelines and seeking continued cooperation as to compliance with those guidelines? Is there a need for Federal legislation? Is preemption, for example, a reason for developing a national legislative set of guidelines?

Dr. FREDRICKSON. I think that's a very important question to all of us, Mr. Thornton.

Mr. THORNTON. Go ahead.

Dr. FREDRICKSON. The hazards of this kind of work remain hypothetical. Yet, we still don't know whether some of those imagined or hypothetical hazards might not materialize.

The fact that we still don't know means that it is reasonable to continue with some prudent guidelines that are flexible, in congruence with scientific knowledge, and reasonably enforced.

How do you enforce a common set of standards in this rapidly moving area? This remains probably the outstanding question and problem we have in the governance of science today.

It is my considered belief after a great deal of involvement in this problem that we really must all agree to proceed under the same rules and the same set of guidelines, or we shall actually be performing a charade.

I believe that the simplest possible way to extend for a reasonable period of time the assurance that we will all follow the same guidelines means that we may have to have legislation. I applaud the legislation that can do this with the minimum of entailment of excessive regulatory activity, which will allow the maximum of discretion of reasonable and responsible people in enforcing it.

I think part of the experience of the past year has particularly taught me that the creation of a bureaucracy centrally to administer



the guidelines is in the long run impossible. We have to have some limit to federalism in this matter. I think that means that there must be a great deal of responsibility at the local level.

Now, the level of regulatory activity that we need is the level that will permit people to make decisions on the basis of explicit and predictable standards that are adhered to in all communities. That latter requirement, the one to allow this to be done sensibly at the local level, actually enforces the need that there be a set of common standards. This brings us back to our first question, that maybe the only way to get those is a reasonable piece of legislation which can be limited, as H.R. 11192 proposes, until we have gone a few years further in the great experiment to learn just how much regulation is really necessary.

Mr. THORNTON. I asked Dr. Handler this morning a question that I would like to direct to you.

I asked him if there were a danger or a risk that we as legislators might be releasing a new kind of "organism" (legislation) when we undertake to regulate scientific inquiry which may with regard to the present proposed legislation. But if the "organism" (legislation) were to escape from the laboratory, then the country might begin to express its concerns and alarms about other fields of research and decide that since we had this institution (recombinant DNA legislation) in place that it would be a suitable place to regulate the scientific research in some other area which might at that moment be considered as having great potential risk or fear.

Do you perceive any concern about this?

Dr. FREDRICKSON. I have it rather constantly with me. I think that's a form of recombinant that needs to be contained very severely. That is why I think the intent of this piece of legislation must be as narrow as possible and the discretion should be there to allow a maximum of flexibility and freedom of scientific inquiry.

Mr. THORNTON. Thank you.

Mr. BROWN. Now, Dr. Fredrickson, a couple of points about the language of the bill:

Now, I notice that in the House bill, title II, the DNA Study Commission involving genetic manipulation that I understand that the Senate language says something about DNA research. We are not using these terms to mean the same thing, are we, in these two bills?

Dr. FREDRICKSON. My interpretation of the two bills with regard to the study commission is that the House provision is somewhat broader than the Senate mandate to the commission. I favor the House approach. If there's going to be a commission, then I think it ought to attempt to deal with the social and ethical aspects of the broader use of genetic techniques with regard to man or genetic manipulation.

I think it would be appropriate to use it for that purpose and that it would have the opportunity to do it along with attempts to learn, with the rest of us, about this otherwise very narrow problem of regulating the recombinant DNA techniques in the laboratory.

Mr. BROWN. We have the correct understanding, do we not, that genetic change can occur through other methods than recombinant DNA processes?

Dr. FREDRICKSON. Yes; that is certainly correct, Mr. Chairman.

Mr. BROWN. Let me ask you a couple of other points or questions:



The commission is specified to contain 13 members from a range of particular disciplines.

Dr. FREDRICKSON. Yes.

Mr. BROWN. It seems to me that the listing was purposely developed to be as broad as possible, but do you see any problems with it being either too narrow or too broad or too exclusive or inclusive?

Dr. FREDRICKSON. I find the language of the House bill for selection of the committee was quite reasonable and it should be no less broad than it is.

Mr. BROWN. With regard to the appointing authority, there is no place here for the speaker of the House to appoint members as a director of something.

Do you think this is a preferable procedure to follow or let the Secretary of HEW do it?

Dr. FREDRICKSON. I think it's consistent with the purposes of the bill to have the Secretary appoint the members.

Mr. BROWN. It runs through my mind in any examination of a complex subject like this that these are situations where we can draw parallels. For example, in the construction industry, almost every major construction undertaking sets up safety committees on the particular site. I am wondering whether this concept of biohazards or safety committee, if it could have application in other areas, or if experience in other areas could have applicability here.

Let me cite two specific examples: There are the problems of radiation and problems of toxic substances. They are similar in their nature.

Can we learn from or in turn can we apply what we are learning in the recombinant DNA problem areas to situations in the other areas?

Dr. FREDRICKSON. I think, Mr. Chairman, what we have the greatest probability of achieving in this whole exercise is a new way to deal with the multitude of problems of which this may be the most unusual or perhaps the most important example. It is a very important exercise. We are trying to educate ourselves as we move in dealing with this very specific problem. I think that is a great virtue in keeping the objective extremely narrow at present until we are sure we are going to be able to handle the small part of such a problem.

Mr. BROWN. One of the things that we do not do adequately in the passage of legislation is to recognize that we are engaged in a learning experience, a scientific experiment, or whatever you want to call it, whenever we pass legislation.

Now, we sometimes think we are more like the Lord on high. But we are not. We are merely conducting an experiment. It is important, as you say, that we conduct the experiment wisely, but to recognize what we are doing and to learn from it in the process. This is the thought that I was trying to get at here.

Now, along the same line, I will pose this question to you:

Do you think it would be desirable to charge the commission specifically with the responsibility of reporting to Congress on the learning process as it might apply to other similar kinds of problems where there is an interface between science and politics?

Dr. FREDRICKSON. Yes.

Mr. BROWN. It could broaden the mandate of the commission considerably and get away from the narrow construction.

Dr. FREDRICKSON. I think it would be very well to consider that.

Mr. BROWN. Perhaps we could put some emphasis on it. You are elaborating in the language of the report as to how we can get the maximum benefit from our moving into a new field of this sort.

Thank you.

Are there any further questions?

Mr. FUQUA. No.

Mr. BROWN. We are very happy, Dr. Fredrickson, to have you with us this afternoon. We are even happier to be able to excuse you at this point, so that we can go vote.

[Questions and answers for the record follow:]

MAY 9 1978



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20014

May 5, 1978

The Honorable Ray Thornton  
Chairman, Subcommittee on Science,  
Research, and Technology  
Committee on Science and Technology  
House of Representatives  
Washington, D.C. 20515

Dear Mr. Chairman:

I am writing in response to your letter of April 17. Enclosed are my responses to the series of questions on which you requested my views. The questions were excellent and addressed important policy matters. My responses are based on the premise that the legislation should not specify regulatory requirements but should permit flexible regulation under the Act by the Secretary of Health, Education, and Welfare. As your Committee Report on H.R. 11192 so cogently states, this legislation must be viewed as an experiment to be conducted wisely in order to determine effective legislative and regulatory mechanisms and whether such mechanisms need to be continued beyond the two years specified in the bill.

I am enclosing for your review a letter I have sent to Congressman Paul Rogers, Chairman of the Subcommittee on Health and the Environment of the Committee on Interstate and Foreign Commerce. In my letter, I emphasize the need for clarification of the Commerce Committee Report (H.R. 11192) on Department responsibilities under the National Environmental Policy Act. Another of my concerns discussed in the letter is that revisions of the NIH Guidelines be completed prior to enactment of the legislation. Were legislation to pass before the revisions are completed, unnecessary regulatory burdens would be imposed because the current Guidelines would be the standards promulgated under the new law while the efforts of the past year and a half to develop revisions would be put in abeyance.

I want to thank you again for the splendid work you and your Subcommittee have done in this most difficult but crucial area of science policy. The reports and hearing records of your Subcommittee have been outstanding, and I especially want to commend the work of Dr. Gail Pesyna of the Subcommittee staff and Dr. Jim McCullough of the Congressional Research Service.

/ Thank you very much.

Sincerely yours,

Donald S. Fredrickson, M.D.  
Director

Enclosures

RESPONSES BY DR. FREDRICKSON TO QUESTIONS POSED  
BY THE SUBCOMMITTEE ON SCIENCE, RESEARCH, AND TECHNOLOGY  
OF THE HOUSE COMMITTEE ON SCIENCE AND TECHNOLOGY

1. Would you comment on the statement in the Commerce Committee report that "it is the Committee's understanding that the Secretary will complete and file an EIS on all the guidelines and administrative regulations, as expeditiously as practicable, even after promulgation of the administrative regulations....Furthermore, NEPA would apply to any revisions either of the initial requirements promulgated under section 102(a)(2), or of the administrative regulations under section 102(d) of the Committee bill." Do you have any additional comments you wish to add for the record with regard to NEPA and its application to recombinant DNA regulation?

I am very troubled by the statement cited above, for it might be construed to mean that the Department is required to file an environmental impact statement (EIS) on all standards and regulations under the Recombinant DNA Act. I have written to Paul Rogers, Chairman of the Subcommittee on Health and the Environment, urging a clarification of the Committee report on this point.

As I stated at your Subcommittee hearing on H.R. 11192, under the requirements of the National Environmental Policy Act (NEPA), it is more precise to say that the Department will conduct an assessment of the environmental impact of the standards and regulations. Based on the assessment document, a determination will be made whether an EIS is specifically required. And, to the extent the implementation of NEPA parallels actions already taken in developing the Guidelines, an EIS on the implementation would presumably incorporate, rather than duplicate, the EIS already prepared on the Guidelines. The clarification that the Committee on Science and Technology made on this point in its bill report is most appreciated.



2. Do you anticipate any problems in identifying the legally responsible entity in recombinant DNA research projects?

It is NIH policy that all grants and contracts are made to the institution rather than the individual investigator. For purposes of the NIH Guidelines and research projects thereunder, the institution is the responsible legal entity. Under proposed revisions of the Guidelines that I am considering, that responsibility will be more clearly defined. Thus, I do not anticipate any problems in this area.

3. Are you satisfied with the definition of "recombinant DNA" that is contained in H.R. 11192?

The definition of recombinant DNA contained in H.R. 11192 is satisfactory. As you may know, I am currently considering proposed revisions of the Guidelines that may include changes in the definition. However, the flexibility provided in H.R. 11192 by the authority for exemptions should permit any necessary adjustments in the definition contained in the bill. The report of the Science and Technology Committee suggests, and we agree, that the definition in the Act be made consistent with that of the revised Guidelines.

4. Do you perceive any problems with the interpretation of Injunction Authority (Section 104) as given in the report of the Commerce Committee?

The House Commerce Committee report indicates (pages 22-23) that anyone may sue under section 104 to ensure enforcement of the Guidelines so long as they are able to allege some threatened injury. I am troubled

by this provision, for there exists the possibility that individual investigators and their institutions might be subject to the expense and harrassment of frivolous litigation. DHEW, however, has a policy of supporting private rights of action.

5. How far do the current NIH guidelines go in covering the safety standards for large-scale manufacturing processes involving recombinant DNA? Are special requirements necessary? What do you perceive the role of NIH to be in this area?

Current Guidelines prohibit large-scale experiments (e.g., more than 10 liters of culture) in which recombinant DNA is known to make harmful products. Thus, large-scale experiments can be carried out under the present Guidelines if harmful products are not to be made. I am considering proposed revisions to the Guidelines that would permit exceptions to the 10-liter limitation on the basis of scientific and societal benefits and potential risks. At present, special requirements are not necessary in this area, for our experience is extremely limited and no large-scale experiments are being done by NIH grantees and contractors. The potential for this work would be largely in the private sector, and approval for the work to be done under specified criteria would need to be made under the law by the appropriate regulatory agency (presumably the Center for Disease Control).

6. The inspection authority in section 105(a) is permissive. Should periodic inspections of all research facilities be required?

I support the inspection authority in section 105(a), and I do not believe it should be made mandatory. Under the proposed revisions to the NIH Guidelines primary responsibility for review and oversight of recombinant DNA activities would be placed in the Institutional Biohazards Committees. Federal oversight under the legislation may include inspections, but it is unnecessary and unwarranted for inspections to be required.

7. Is there any evidence that members of local biosafety committees have sufficient time, information, and motivation to monitor the conduct of recombinant DNA experiments, including inspecting laboratories? Should local biosafety committees be required to report alleged violations to HEW?

As required by the NIH Guidelines, all institutions receiving NIH support for recombinant DNA research have created Institutional Biohazards Committees. I am impressed by the effort of the local institutions to create effective committees with excellent representation. On the basis of information we have received, the members of these committees have the necessary expertise to monitor recombinant DNA experiments. As proposed by the Recombinant Advisory Committee, I am considering revisions to the Guidelines that would strengthen the mandate of these committees and ensure expertise in occupational and environmental health and safety. Other suggested revisions would require that the biohazards committees notify NIH of alleged violations.

8. Should local biosafety committees be required to:
- a. Undergo periodic on-site visits and audits by Federal agency officials of committees' performance?
  - b. Periodically review all ongoing recombinant DNA research projects?
  - c. Provide incentives for service on local committees?
  - d. Have Federal reimbursement of the direct costs of the committees?

This question raises a number of issues that I have considered as part of the proposed revisions to the Guidelines. I believe generally that the law should not specify requirements for local biohazards committees to perform the functions cited. H.R. 11192 provides for flexibility in regulation, and that is one of its greatest strengths. Thus, I would not require by law that there be periodic on-site visits and audits by Federal agency officials of committees' performance. Clearly, under the regulations such audits would be conducted, but they should not be mandated by law.

As I noted in response to questions 6 and 7, the local biohazards committees, in the proposed revisions to the Guidelines, would have full authority to approve and review all ongoing recombinant DNA research projects. Such a mandate may indeed be part of the regulations, but again I would not require it under the law.

It has been suggested by some that NIH directly reimburse the costs associated with institutional biohazards committees, including payment



of members. However, institutions receiving NIH grants and contracts are already paid for their indirect costs, which cover the operations of the institutional biohazards committees. I see no virtue in mandating direct Federal payment for these committees that would separate them out from other indirect costs of the institution.

9. Are there adequate safeguards within the Administrative Procedures Act to protect data submitted to local biosafety committees and to the Commission established by Title II from disclosure of data prior to determination of the applicability of the Freedom of Information Act?

I believe there are adequate safeguards to protect data submitted to local biohazards committees and to the commission. All members of the institutional biohazards committees and the commission would be subject to 18 USC 1905, which prohibits the disclosure of trade secret information.

10. What procedures should be followed in making determinations of confidentiality? What should the rights of the submitter be prior to government disclosure?

There are a number of standard procedures developed by regulatory agencies such as the FDA which would be followed in making determinations of confidentiality in the regulations implementing H.R. 11192. Under regulations the rights of the submitter prior to Government disclosure would be specified, as they are, for example, in regulations under FDA.

11. Some individuals have expressed concern that the exemption authority granted to the Secretary in section 102(b) will prompt numerous requests from scientists who would like to have individual projects exempted from the regulations. Does the Administration anticipate such a situation arising? How could we guard against its happening?

In light of the administration of the NIH Guidelines over the past year and a half, I do not believe there will be numerous requests from scientists to have exemptions granted by the Secretary under the proposed revisions of the NIH Guidelines. Further, the NIH Guidelines and regulations developed under this Act would ensure proper procedural protection and would specify standards to be met before exemptions would be granted.



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20014

May 5, 1978

The Honorable Paul G. Rogers  
Chairman, Subcommittee on  
Health and the Environment  
Committee on Interstate and  
Foreign Commerce  
House of Representatives  
Washington, D.C. 20515

Dear Mr. Chairman:

I strongly commend you and Congressman Staggers for working effectively to develop an interim bill (H.R. 11192) that provides for sensible regulation and public oversight. There are two aspects concerning the legislation that I believe I must call to your attention.

As you know, the National Institutes of Health filed an Environmental Impact Statement on the Recombinant DNA Guidelines in October 1977, and we are presently conducting an assessment of the environmental impact, if any, of the proposed revisions. In the report of the Commerce Committee accompanying H.R. 11192, the following statement is made on page 20: "It is the Committee's understanding that the Secretary will complete and file an EIS on all guidelines and regulations, as expeditiously as practicable, even after promulgation of the administrative regulations. . . ."

I am troubled by that statement in the Committee Report and would appreciate the opportunity to discuss its implications with you. As I understand it, the National Environmental Policy Act requires an assessment of the environmental impact of the standards and regulations. A determination will then be made on the basis of the assessment document whether an EIS is specifically required.

The other aspect of the legislation that I would mention is the extreme importance that I attach to having revisions completed on the NIH Guidelines before legislation is passed and regulations implemented. The revisions under consideration include changes for

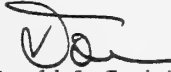
Page 2 - The Honorable Paul G. Rogers

which there is overwhelming sentiment. Indeed, the most recent expressions of support for revisions occurred at the public hearing of the Advisory Committee to the Director, NIH, in December. That hearing was devoted to a public review of the revisions proposed by the Recombinant Advisory Committee, the technical committee responsible for developing and revising the Guidelines. My decision on the revisions with an environmental impact assessment should be completed about June 1 and promulgated for public comment over at least 30 days.

Thus, we are moving to promulgate these revisions as rapidly as is consistent with the Administrative Procedures and Practices Act, so that we can avoid the unnecessary regulatory burdens that would be imposed if the current Guidelines were to become the standards under the legislation. Enactment of legislation prior to completion of this process would put in abeyance the enormous effort over the past year and a half to develop the necessary revisions in the standards and implementation of the Guidelines.

I want to thank you again for the outstanding work you have done in this most difficult science policy area. I also want to commend both the cooperativeness and skills of Steve Lawton and Burke Zimmerman, with whom I have had the privilege of working very closely.

Sincerely yours,



Donald S. Fredrickson, M.D.  
Director

[Whereupon, at 2:55 o'clock p.m., the Subcommittee adjourned.]



# APPENDIX

[Whereupon, at 2:55 p.m., the subcommittee adjourned.]

UNIVERSITY OF WASHINGTON  
SEATTLE, WASHINGTON 98195

*Program in Social Management of Technology*

April 10, 1978

Congressman Ray Thornton  
Chairman, Subcommittee on Science, Research and Technology  
Committee on Science and Technology  
U.S. House of Representatives  
Washington, D.C. 20515

Dear Congressman Thornton:

I understand that your subcommittee will be holding hearings on HR 11192, "The Recombinant DNA Act," which was introduced by Congressmen Staggers and Rogers in February. For the past fifteen months, I have been a member of the Recombinant DNA Biohazards Committee at the University of Washington, a ten-member group charged with having general oversight responsibility in regard to all aspects of this research as conducted at the University of Washington. I am an associate professor at the university in the Program in Social Management of Technology; my areas of teaching and research (both here and previously at Cornell) include technology assessment, environmental law and policy, risk analysis, and social values and technological change.

I am disappointed that the House Committee on Interstate-Foreign Commerce apparently held no hearing on the subject legislation, and acted in unseemly haste in reporting the bill out. In general, regulation of recombinant DNA research to date has been characterized by very limited opportunities for meaningful formal input on the part of scientists in other but related disciplines, non-scientific professionals with relevant perspectives, and citizens. The guidelines developed by the NIH are essentially the product of deliberations conducted by those who will be regulated by them; thus the situation has potential conflicts of interest built into it, and should be as suspect as the attempts by industry trade associations to forestall meaningful government regulation by the adoption of voluntary industry standards. Considering the fact that the primary issues raised by this research are not solely scientific or technological but have major public policy components, this situation goes against the grain of the past decade's academic research and findings in the area of "science, technology, and public policy" as well as recent political experience regarding the beneficial effects of citizen participation in many fields.

As a result, I wish to offer you my opinions on the pending legislation. These arise both from my professional studies and from my experience as a member of a local biohazards panel.

I strongly object to the federal preemption provisions contained in section 106. As one who has followed the issues in this area closely, I am aware of no real justification of federal preemption. In fact, I believe that the

Congressman Ray Thornton  
 April 10, 1978  
 Page 2

provisions for such a preemption are logically contradicted and undercut by the provisions in section 202 (1) (D) that the Commission be established by the bill to study the necessity of Federal preemption. If there is enough uncertainty about the need for such preemption as to require such a study, and in the absence of any compelling evidence to date that preemption may be necessary, I believe that the preferable course of action would be to permit supplemental state and local regulation not inconsistent with those imposed federally, until such time as the need for preemption is actually demonstrated.

I have heard of only one argument which would appear to support the position of precluding state and local involvement in DNA regulation--the fear that undue burdens may be placed on scientific work in particular locations. There is so far no proof (and indeed, hardly any claims) that this has yet occurred. On the contrary, local experience shows that the involvement of local regulatory bodies can provide aspects of a regulatory scheme which would be difficult, if at all possible, to achieve under federal preemption. In order to support this last statement, allow me to offer several specific examples obtained from the work of the U.W. Recombinant DNA Committee.

- (A) Development of procedures for certifying actual laboratories as meeting the levels of physical containment claimed for them;
- (B) Participation in the development and certification of training programs to insure that researchers carrying out recombinant DNA work are aware of what the regulations require of them, and have the capabilities to carry out those requirements;
- (C) Passing on the qualifications of specific researchers to actually carry out the research problems. This has been important in regard to the more risky types of experiments. For instance, we are presently in the process of assuring ourselves that researchers who are proposing to do P-3 experiments are adequately trained in relevant micro-bacteriological techniques.
- (D) The imposition of a moratorium on considering P-3 level research proposals (for approximately 18 months) in order to assure that researchers in relevant areas, members of the biohazards panel, institutional biohazard safety inspection personnel, and the general public build up sufficient experience with less risky forms of experimentation in order to have the capabilities to reasonably assess, perform, and monitor more risky experiments;
- (E) Requiring that all meetings of the DNA biohazards committee be conducted in public; reserving for executive session only the final discussions and votes on particular research proposals; and that researchers prepare a summary of their research proposals in lay language to maximize the ability of persons (non-geneticist professionals as well as citizens) to understand the proposals and their public policy implications, and allowing open questioning of the researchers by members of the panel and members of the general public;

Congressman Ray Thornton  
April 10, 1978  
Page 3

- (F) In a proposal to investigate the genetic production of enzymes in yeast which regulate the conversion of glucose to alcohol, we were concerned about the potential production of E-coli which would have augmented capabilities for producing alcohol. We therefore qualified our approval by requiring the researcher to check the alcohol production of the mutant E-coli produced, and to return to the committee for further deliberations if it was two or more times greater than the natural production of alcohol by the bacterium. This was necessary because the locations for the genes producing the alcohol and suppressing the alcohol production have not been adequately mapped, and so there was the danger that the recombination might produce a species with greatly augmented alcohol production abilities;
- (G) We have conditioned approval of proposals involving the use of non-transmissible plasmids to require checking that they remain non-transmissible after cloning;
- (H) We have conditioned approval of proposals which involve the use of virulence genes to require their being split in ways which would increase the probabilities of the fragments being kept non-virulent;
- (I) We have conditioned approval of an experiment involving genetic transfers from yeast to E-coli and then back into yeast in order to study what the effect has been, on the prior approval by the NIH of the use of yeast as a host system.

In situations such as the latter examples given above, I believe that the regulatory mechanism should facilitate fine-grain tuning to the particular requirements and risks of the specific experiments being proposed; I am afraid that a federal preemption scheme would not provide sufficient personnel and time to allow such specific attention to be applied as adequately as can be done where local regulatory bodies act within a federal framework.

In addition, the provision for federal preemption seems to be operating on assumptions which do not sufficiently distinguish between the concepts of "risk" and "safety" as discussed in the book *Of Acceptable Risk* by William Lowrance (presently special assistant to the Under Secretary of State for Security, Assistance, Science, and Technology, and a participant in the March 1977 Academy of Sciences forum on recombinant DNA). Risk is a relatively objective measurement of hazards whereas safety is a subjective expression of the level of risk which is acceptable to a population. In other words, even if the various risks associated with DNA experimentation can be determined once and for all by a single (presumably federal) body, the question of safety involves many value issues which a local citizenry and their representatives are better able to ascertain than is a federal agency.

Congressman Ray Thornton  
April 10, 1978  
Page 4

In regard to another matter completely, I am unhappy with the indicated composition for the Commission proposed by Title II of the legislation. At the very least, there should be representation by laboratory workers and technicians involved in this research, by educated and knowledgeable citizens, and by persons knowledgeable in the area of science and public policy. (The same comment is true, of course, for the composition of local biohazards panels, which are not required by the existing guidelines to be sufficiently diverse and representative of various perspectives and sources of wisdom on the issues they are to consider.)

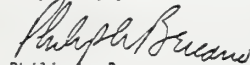
I believe there is no justification whatsoever for the provision in section 102 (E) for exempting recombinant DNA regulation from the requirements of the National Environmental Policy Act. In fact, the operations of the NIH to date in regard to NEPA have been fairly scandalous; a final environmental impact statement on the original guidelines has yet to be produced, and decisions have been taken which have potentially major ramifications without any impact statement provisions being followed (for example, on March 9, 1978 a subcommittee of the NIH approved the use of yeast as a host for recombinant DNA work in certain circumstances).

The proposed legislation does not address issues of patentability and who should have rightful claim to the benefits from research in this area. This is a particularly important set of issues now, because the General Services Administration has recently amended federal procurement regulations to permit universities and profit-making firms to get increased commercial benefits from federally financed research. Members of the public have repeatedly expressed to me, in my capacity as a member of a local DNA biohazards committee, their belief that federal law and regulations already require that the results of federally financed research be in the public domain, and I have no doubt that were they to be aware of the existing legal situation they would be urging a change in that direction.

In summary, let me refer again to the issue of preemption which I believe is among the more important of my views noted above. I believe that the existing language of section 106 is far too stringent (requiring that the Secretary find that a proposed local requirement "is necessary to protect health or the environment"). That is almost an impossible burden of proof for anyone to sustain. I believe it should be sufficient that a locality shows that it has material and relevant reasons for participating in the regulatory process, reasons which go towards its perceptions of safety, its knowledge of local conditions, its perceptions of mores and traditions in the locality regarding enforcement and monitoring of specific institutions, and the like.

Thank you very much for this opportunity to express my views on this important piece of legislation.

Very truly yours,



Philip L. Bereano  
Associate Professor

PLB:r1



## REMARKS BEFORE RAC MEETING

April 27, 1978

The NIH Guidelines for Recombinant DNA Research were issued in June 1976. Subsequently, other national guidelines for regulation of these controversial and promising techniques have been issued by Britain, Canada, the Soviet Union, and several other European countries. Recombinant DNA experiments have continued in hundreds of laboratories around the world. The subject has been discussed and debated in countless meetings. In the United States, at least, the public has been consulted no less than the scientific community through formal hearings and publication for comment of guidelines, proposed revisions and environmental impact statements. One of the most important latter-day developments has been the careful scrutiny, from a very broad point of view, of the premises upon which the Guidelines were adopted. Thus the molecular biologists, who first questioned the safety of recombinant research, now have had greater opportunity to consider their concerns in the company of many experts on infectious disease, epidemiology, viruses, plants, laboratory safety practices, ecology and other relevant disciplines.

From all of these activities have emerged some important facts:

- No evidence has come to light that the thousands of individual laboratory applications of techniques for DNA recombination over the last 5 years have yielded a product harmful to man or the environment; examples of useful knowledge obtained through such techniques continue to accumulate.

- No new scientific evidence, not considered in the promulgation of the guidelines, has emerged to support the fears that the use of these techniques will create a harmful product.
- The probability of doing harm with laboratory recombination of genes has not been, and never will be reduced to zero. We are approaching a point, however, where the burden of proof is shifting more and more to those who would restrict such activities. The careful interpretation of evidence obtained before and after June, 1976, has reduced to inconsequential levels the probabilities that E. coli K-12, the host most used in recombinant DNA experiments, can be converted to an epidemic pathogen. Much of the relevant data and their discussion by experts is now available in the published proceedings of an NIH-sponsored meeting in Falmouth on June 20-21, 1977. (J. Inf. Dis., May, '78)
- Analysis of existing knowledge of viruses by two groups of experts indicates that the risks of cloning viral DNA in a bacterium like E. coli is not greater, and usually much less than, the risk of handling the parent virus itself. The data supporting these conclusions are now available in the report of the Ascot (England) meeting on January 26-28 sponsored by NIH and EMBO and the report of a working group at Bethesda on April 6-8.

- A group of agricultural scientists meeting on March 20-21, 1978, under the auspices of NSF, the Department of Agriculture, and NIH, have concluded that containment conditions for incorporation of DNA from plant pathogens or virus in E. coli K-12 are unjustifiably high. Their data will be presented to you during this meeting and you will determine whether further changes in the Guidelines should be made at this time.
- There is overwhelming sentiment for exemption from the Guidelines of experiments involving most "self-cloning" systems or pairs of harmless organisms which transfer genes in nature. (cf. transcript of public meeting, Director's Advisory Committee, NIH, December 15-16, 1977.)
- There is universal sentiment for permitting the Director, NIH, discretion to exempt certain experiments from the provisions of the guidelines, especially when this will permit knowledge to be gained bearing on maintenance or further revision of the Guidelines.
- There is a deepening concern in the scientific community, shared by those who have borne the administrative responsibilities within the NIH, that the locus of responsibility for use of the Guidelines must shift further toward the institutions conducting this research. The present requirement

for approval from NIH before an experiment may proceed has caused delays unjustified by proof that safety has been enhanced as a result of them.

- Analyses of the available Guidelines prevailing in Britain and Western Europe and of how they are being interpreted by genetic manipulation advisory groups, indicate that some experiments are permitted there which are not permitted in America. More importantly, there is no factual basis upon which to defend the greater stringency of the U.S. (NIH) Guidelines.
- Movements to pass legislation to convert the NIH Guidelines to regulatory standards have begun again in Congress. There is ample indication in the Congress that the NIH Guidelines of 1976 represent an undesirably stringent and overly broad set of standards for such regulation. Unless revised standards are in effect, however, the 1976 Guidelines will be converted into law.
- The revisions proposed by the Recombinant Advisory Committee in September 1977 embody many of the changes now perceived to be desirable. There are additional revisions which were mandated by the public hearing in December 1977, however, and these are subject of the RAC meeting today.



It is imperative that at this meeting final decision be reached on the recommendations for this current set of revisions. NIH is still left with much more to complete. The Director, NIH, must make his final decisions and subject the resulting changes to an environmental impact assessment. If he concludes that such assessment indicates a significant impact of such revisions on the environment, a draft environmental impact statement must be prepared and published. With or without the latter, the proposed revisions of the Guidelines must be published, accompanied by the environmental impact assessment, and a decision paper explaining the revisions.

This publication will be followed by a period of at least 30 days for public comments. The issuance of final revised guidelines will follow.

#### The RAC Agenda

At this meeting the RAC must address, if possible, all of the following areas of proposed revision: (1) revised definition of the scope of the guidelines, including discussion of the Tabs A, B, and C arising from the Spizizen committee deliberations and construction of the first list of exempted exchangers, (2) the selected issues addressed to it by me, including revised Roles and Responsibilities, (3) experiments with Viral DNA or Viral Vectors, and (4) experiments involving plant pathogens or viruses.

On April 12, 1978, I mailed you a set of comments and queries on the proposed revisions of the Guidelines. The "Issues for the Committee's Consideration" begin on Page 2. I would like to illuminate briefly my views on some of these matters. I hope you will also air questions you have for me about them as we go along.

### Exemptions

Everyone seems to agree that the Guidelines now cover activities which should be exempted. First is the handling of DNA outside of organisms. Such "naked" DNA has been handled in laboratories for many years and one guesses that all possible genetic recombinations have long ago occurred in the waste flowing from such sources. The 1976 Guidelines, however, contain a prohibition (ii) which forbids deliberate formation of recombinant DNAs containing genes for the biosynthesis of potent toxins. There is no need to repeal this prohibition at present. In fact, with one possible minor exception,\* I do not believe it wise to remove any of the explicit prohibitions at this time, because the Director will have discretion to lift them on a case-by-case basis. Therefore, save for the earlier prohibition, recombination of other DNA per se is now (proposed to be) exempted from the Guidelines.

The second class of experiments exempted relate to DNA sequents from a single source. Examples of these are excisions of DNA of a host such as SV40 virus and its insertion into eukaryote able in tissue culture. Whether such deletion experiments involving a single source are actually covered by the '76 Guidelines has been uncertain. There is little, if any, basis for presuming them to be harmful.

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\*The prohibition on use of recombinant DNAs derived from oncogenic viruses classified by NCI as moderate risk will have to be altered if one of the recommendations of the virus group (that concerning VSV) is accepted.

The third class of exemptions involve the recombinations of DNA such as from plasmids already found in the host. Many of these involving E. coli K-12 are permitted at minimum containment (P1-EK1) in the '76 Guidelines. Other hosts and their plasmids are also exempt, unless they are covered in the prohibited experiments. The second and third class of exemptions involve systems that are often referred to as self-cloning.

The fourth class involve donor-host pairs known to exchange genetic material in nature. Much trouble has been caused here by desire to avoid ambiguous words or phrases such as "normal" or "non-novel." "Physiological process" has been selected to stand in for them. The criteria for eligibility to be placed on such a category need to be indicated. The first list of such exempted pairs should appear in the set of revisions to follow this meeting.

A fifth class of exemptions is permitted, primarily to include combinations that are judged to be quite safe even if not exactly "normal" or "non-novel." It is important to clarify what is meant by "appropriate" notice and opportunity for public comment referred to in exemption V (in Tab C). It is not expected that public hearings will be held on every addition to exemptions classes IV, or V. It may be possible to give advance public notice of the intent to consider them at a forth-coming RAC meeting. If not, the decisions will be published and a period, usually 15 to 30 days, allowed to elapse before they become effective. Such opportunity for public comment is appropriate respect of "due process" in such class actions.

I will address only a few other considerations in my letter to the RAC.

The institutions governed by these guidelines now will include, notwithstanding agreements among federal agencies which greatly extend their coverage, all institutions receiving any NIH funding for recombinant DNA research. We have not extended it to all institutions receiving any NIH funds. Suppose that NIH funds were supporting development of a cancer drug in a profit-making laboratory. That another independent branch of this same private industry were to engage in recombinant DNA research. It is not practical or even realistic for NIH to pretend to participate in governing this latter activity except on a voluntary basis.

Another matter on which I would like the Committee's advice is its willingness to certify new host-vector systems and assist in consultation on interpretation of the Guidelines where proprietary information is involved. Unless NIH, as it was urged to do so in the public hearing in December, or some other agency provides opportunity for privately supported researchers to obtain such service, there will be no possibility of voluntary adherence to the Guidelines by all researchers in this country.

Finally on matters of Roles and Responsibilities, I would emphasize that I am convinced that more responsibilities must devolve upon the principal investigator, institution and its biosafety committee. There are certain conditions inherent on the proposed shift of authority:



- a common set of guidelines, that clearly delimit the discretion permitted locally.
- ability within the biosafety committee to determine compliance with the guidelines.
- recognition that sanctions will be used to guarantee a competent and responsible exercise of local authority; and that, if actions approved are found inconsistent with the guidelines by NIH review, the experiments not in compliance must close.
- avoidance of conflict of interest and representation of community interests in the membership of biosafety committees.

These are some of my perceptions. I believe it is important for you to know them as you proceed independently to make your recommendations.

I have one other statement. This is the last of the meetings to be chaired by Hans Stetten. He has borne this heavy responsibility since the day NIH entered this issue at the invitation of the Asilomar participants. Although he may not agree, I believe no more fortunate a choice of chairperson could have been made. I speak not only for the scientific community, but for everyone concerned, in acknowledging our gratitude to him for the honesty, common sense and dignity which he has publicly maintained, and for the outrage and doubts which he has confined to private expressions.

I should also again wish to acknowledge my debt, indeed also everyone's debt, to those of you and to your predecessors who have borne the arduous duties of the RAC. This experiment in which we have all engaged will not have been for nothing.

INTRODUCTORY REMARKS 1/

by

Donald S. Fredrickson, M.D. 2/

It gives me great pleasure to introduce Dr. Har Gobind Khorana, Alfred P. Sloan Professor of Biology and Chemistry at the Massachusetts Institute of Technology. He was born in Raipur, India, and received his Ph.D. in organic chemistry from the University of Liverpool in 1948.

On this day, five years ago, Dr. Khorana received the Willard Gibbs Medal of the American Chemical Society for his outstanding research on the synthesis of polynucleotides and on the nature of the genetic code.

Indeed, since 1960, Dr. Khorana has received over two dozen awards from scientific organizations in several countries, including the U.S., Canada, India, West Germany, and Sweden. He received the 1968 Nobel Prize in Physiology or Medicine, along with Marshall Nirenberg of NIH, and Robert Holley of the Salk Institute.

He will lecture tonight on "Total Synthesis of a Biologically Functional Gene."

Dr. Khorana.

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1/ NIH Lecture, Masur Auditorium, 8:15 p.m., May 10, 1978.

2/ Director, National Institutes of Health, Bethesda, MD.

## REMARKS

at the

1978 NIH Asian-American Cultural Program \*

by

Donald S. Fredrickson, M.D. \*\*

Thank you, Phil. May I compliment you on the very fine program you and your Committee have arranged for the 1978 Asian American Celebration at NIH, in this the Year of the Horse?

I am delighted to welcome all of you here and to have you share with me the cultural richness of this sixth annual program.

The week before last, while in San Francisco, I read in the CHRONICAL that a twelve year old pre-medical student at the University of Southern California aspired to be the first lady President. Were this to happen, it could be the Nation's gain, but on the other hand, it could be a loss to our world of biomedical research.

In light of our Asian-American program, I thought it especially interesting to note that her mother is Filipino and her father, Chinese.

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\* Held at the National Institutes of Health in the Clinical Center Masur Auditorium on May 11, 1978.

\*\* Director of the National Institutes of Health, Bethesda, Maryland 20014.

During the year, we have three other ethnic programs similar to this one: Black History, Hispanic, and Native American.

I believe when we think of ethnic groups we must remind ourselves that our country is made up of a number of ethnic groups, originally foreigners, representing dozens of nationalities. Anthropologists say that even our native American Indians came from the Asian continent.

We are aware that the Asian and Asian-Americans have a lively and active cultural life. We at NIH are very familiar with their great contributions to biomedical science and science in general. And their rich cultural achievements as well, are no surprise to us.

Just last night, an Asian-American Nobel laureate lectured in this auditorium. He was Dr. Har Gobind Khorana who shared the prize with one other and our own Marshall Nirenberg.

Three years ago, more than 130,000 people arrived in this country from Southeast Asia to begin a new life. Since then 70,000 more have arrived and plans are shaping up to admit 20,000 annually.



While many have successfully made the transition and adjustment to our way of life, many have not. It will take time. But like other Asians before them, and those ethnic groups from other parts of the world who have made a new life here, their strength, character, traditions, customs, experience, brilliance, and efforts will also play an important part in the continued growth and development of the United States.

Who knows what great achievements will result from the experience, minds, talents, and efforts of these new "Americans"?

We will have an opportunity tomorrow night to witness two traditional ceremonies of Southeast Asia--one Vietnamese and the other Laotian.

I am very proud of our Asian-American employees who are part of our fine NIH family. And I appreciate the efforts and contributions of our Asian colleagues who spend time in their careers with us here in Bethesda.

Today and tomorrow, we at NIH are honored to be able to share the cultural life of our fellow Asian-Americans and the Asian community.

## INTRODUCTORY REMARKS\*

Donald S. Fredrickson, M.D.\*\*

It is a great pleasure to welcome all of you tonight to the annual Dyer lecture. This is the twenty-seventh in a series established in 1950 to honor the late Dr. Rolla Eugene Dyer upon his retirement as Director of the National Institutes of Health. Dr. Dyer served as NIH Director from 1942 to 1950--a time of substantial expansion and growth for this institution. He was deeply involved in planning the construction of one of the world's foremost research hospitals--the NIH Clinical Center--whose 25th anniversary we are commemorating this year.

Although Dr. Dyer's administrative career was truly brilliant, his contributions to medical research were equally outstanding. His most significant achievement was in endemic typhus--he showed how the disease is spread and eventually developed a vaccine to protect against infection. His studies furthered scientific knowledge of other infectious diseases as well, including influenza, scarlet fever, Rocky Mountain spotted fever, bubonic plague and Q fever.

In honor of this great man, I am especially pleased that tonight's speaker is Dr. Robert M. Chanock who is one of the most distinguished scientists on our own intramural staff, and a world renowned expert in infectious diseases.

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\*Dyer Lecture, Masur Auditorium, 8:15 p.m., May 31, 1978

\*\*Director, National Institutes of Health, Bethesda, Maryland

Editorial note: Delivered by Dr. DeWitt Stetten, Jr., Deputy Director for Science, NIH

Dr. Chanock received a B.S. degree in 1945 from the University of Chicago and his M.D. in 1947 from the University's School of Medicine. He has authored more than 240 scientific papers and is the recipient of numerous awards.

Dr. Chanock is currently Chief of the Laboratory of Infectious Diseases of the National Institute of Allergy and Infectious Diseases. His research career has been devoted to the study of viral respiratory diseases in an effort to develop more effective methods of prevention and control.

In 1957, he made the first isolation from children with croup and pneumonia of a virus that he later named the Respiratory Syncytial virus. This agent has been found to be the single most important viral pathogen in infancy. Later, he organized studies that led to the identification of the major cause of pneumonia in military recruits, an organism he called Mycoplasma pneumoniae. From this work, a successful method of treatment for this illness resulted. In addition, Dr. Chanock was one of those instrumental in conceiving a new immunization technique to prevent Adenovirus type 4, which had been the causative agent of yearly epidemics.

More recently, his attention has turned to the study of influenza, perhaps the most important of the viral respiratory diseases. His pioneer study of temperature-sensitive mutants of the influenza virus has led to recent vaccine trials that hold promise for the eventual control of worldwide influenza epidemics.

Tonight, Dr. Chanock will speak to us on the "Influenza Virus--Recent Insights and Prospects for Effective Control."

Dr. Chanock.

FEDERALISM IN SCIENCE: HOW MUCH IS ENOUGH? 1/

by

Donald S. Fredrickson, M.D. 2/

It is some time ago that the title for this talk was tossed back to the printer, a hasty response to his impatient demands. It is an ambitious-sounding double feature of a title. What is "Federalism" in science, anyway? If it be the support of research by the government, could there be too much? Or ever even enough? I ask, "What is the answer?" You think, "What is the question?" We begin uncomfortably the classic dilemma of Miss Gertrude Stein.

"How much Federalism in science is enough?" Let us hasten to put some limiting definitions around the nouns. "Science" is the easier of the two. There are two usual meanings: the body of knowledge and the process by which it is developed and constantly changed and expanded. For my purposes, I will concentrate largely upon the process. Science, moreover, is a vast terrain, and I am concerned here with only one relatively small, though highly active, region known as molecular biology.

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1/ Delivered at Mt. Sinai Alumni Day, Mt. Sinai, New York, New York, on Thursday, June 1, 1978.

2/ Director, National Institutes of Health, Bethesda, Maryland.



Like some other parts of biomedical research, molecular biology is in exquisite bloom today. One of the main reasons for this is the Federalizing of support for it, beginning about 30 years ago. The resulting illumination of the functions of the cell, particularly how they are controlled by genes, will doubtless stand as one of the all-time intellectual achievements of human endeavor.

How ironic, then, that across this very region there should fall the shadow of a darker side of Federalism -- the incursion of central government control over the details of laboratory experimentation. This is a new and jarring kind of encounter with government for biologists, indeed fundamental scientists of most kinds. Here we have a long period of benign neglect, then encouragement and heavy financial support, to be so lately joined by the spectre of bartering experimental freedoms in turn for support.

It is in this very context, however, that a good many professional scientists recently have become more familiar with the several restrictive connotations of "Federalism." One, the more conventional legal meaning, refers to the pre-emption of state or other local jurisdictions by a national statute or uniform code of standards. Another meaning lies in the kinds of administrative or regulatory practices (even in the absence of a specific statute) which can be invoked by government to exert its central control.

The circumstances, moreover, have dictated that some of us make an exhausting and personal--though hardly private--search for the appropriate limits of these kinds of Federalism in regard to a particular problem of this exuberantly successful biology. Perhaps because I have not been encumbered by either apprenticeship in a molecular biology laboratory or formal training in the pursuit of narrow legal questions, I have the illusion of having acquired a better perspective of this scientific issue and how it relates to society's perceptions and use of the law.

At this point we had better descend briefly to a more practical plane. We can return from time to time to philosophical venue.

In my capacity as Director of the National Institutes of Health, I will presently be responsible for issuing a proposed revised edition of the NIH Guidelines for Recombinant DNA Research. The original Guidelines appeared in the Federal Register on July 7, 1976. In more readable type than provided by the Register, they occupy a looseleaf notebook over an inch thick, including the four appendices. They describe in explicit terms the conditions under which scientists are allowed to combine genes from different organisms and insert them into a living host. The guidelines must be followed by every scientist supported by Federal grants or contracts. This, in practical terms, means a majority of molecular biologists in the world today. By the choice of scientists in West Germany, Switzerland, and some

other countries, the Guidelines govern similar research in those countries; they also are not without important influence upon research in the other countries which have adopted similar rules of their own. Not too surprisingly, the Guidelines have been regarded as unmitigated disaster by some scientists who find them too conservative. They have been condemned by others, usually not doing this kind of work, who find them insufficiently restrictive. The forthcoming revisions of the Guidelines has consumed more than a year of conferences, forums, and debates in which the scientific and the non-scientific publics have had equal opportunity to be heard.

What recombinant DNA research is, and how the NIH Guidelines came about, have also been the subject of half a dozen recent books, countless articles in newspapers and other journals. In an era of technology, recombinant DNA also has been notable for outplaying any other specific scientific topic as a subject for hearings in the last two sessions of Congress.

Recombinant DNA technology was hailed as "a qualitative change in the field of genetics," a "new biology," a "revolution in genetic engineering" when first aired at a scientific meeting in New Hampshire in the summer of 1973. And the exploitation of the techniques so far merit the excitement they have generated.

The ability to join together genetic material from any two sources and to propagate these hybrid elements in bacterial and animal cells permits a gene to be amplified many-fold and be "cloned" in a degree of purity and in a quantity sufficient to advance the knowledge of the structure of genes by leaps that were unimagined a few years earlier. Moreover, the new hosts theoretically have the capacity to express such alien genes. Thus, someday it is conceivable that bacteria can be made to manufacture cheaply and in quantity such precious proteins as human insulin or hormones that are secreted by the brain.

Such extraordinary possibilities could hardly exist without their negative aspects. At that 1973 Gordon Conference on Nucleic Acids, the chairwoman included these remarks in her summation of the excitement about the new recombinant DNA techniques:

"Nevertheless, we are all aware that such experiments raise moral and ethical issues because of the potential hazards such recombinant DNA molecules may engender . . . we have a responsibility to concern ourselves with the safety of our co-workers and laboratory personnel, as well as the safety of the public." <sup>1/</sup>

And, acting in this spirit of concern, the scientists then set in motion a series of events. They defined some of the possible hazards envisioned and suggested certain experiments that ought not to be done until an international discussion could be held.

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<sup>1/</sup> Singer, Maxine, in Research with Recombinant DNA, NAS Forum, March 7-9, 1977.



They also caused to be held a now-famous conference at Asilomar, California, in February 1975, at which was reaffirmed both the advisability of prohibition on certain experiments and the necessity of the matter being deliberated by government bodies representing the interests of society at large. The scientists also requested NIH to develop rules or guidelines which might govern the use of recombinant DNA techniques.

Following dissemination of the Asilomar meeting, the fuller implications of the conclusions reached by the scientists took a few months to be absorbed. By the time that the Recombinant Advisory Committee had completed the drafting of the Guidelines, a full range of opinions about the benefits and the hazards of the research had been aired. Most of the comments were thoughtful and fair; some were self-serving and a few were irrational. There was denying the potential for benefit, but the fear that forbidden biological barriers were to be transgressed was unsettling. A lack of data--and, as events would subsequently prove, a lack of serenity for careful analysis--gave the hypothetical risks an excessively frightening dimension.

Befitting the importance given the matter, the development of the Guidelines and its accompanying Environmental Impact Statement--the first ever published on a subject restricted to basic laboratory research--was accompanied by a full dress display of the Federal Administrative Practices Act. A perceived weakness of the Guidelines was their applicability only to the use of recombinant DNA techniques by scientists supported by

NIH grants. By agreement reached by all Federal agencies, the rules were made to cover all government-supported research. Such privately supported research as might take-place could <sup>be</sup> only voluntarily covered by the Guidelines, however, and Congress shortly began to consider legislation that would set the Guidelines as a national standard. A flurry of local actions threatening to adopt city ordinances or state laws to cover the same activities added a special feature to the Congressional debates. It was, and still is, the question of whether any Federal law regulating recombinant DNA research must pre-empt local standards. Some see pre-emption the only reason for a Federal statute to regulate science as a protection against interruption of a truly international quest for truth by the arbitrary action of a single community. The opposite camp see as intolerable the Federal government's pretension to limiting the degree of protection a community shall establish against a risk.

This is the old argument of Federalism in American law, coeval with the establishment of the Constitution and nothing new . . . except, of course, to biology which is mainly concerned with far different kinds of laws. It was high time, I learned upon consultation, to bone up on Swift vs. Tyson, Erie vs. Tompkins, and any other object lessons in the proper limits of Federalism in the law, as a prelude to the question of how much is enough for science.

Unfortunately for the students at Yale, Grant Gilmore retires this year as a Professor of Law. Fortunately, for all of us he has left at least one delightful book, entitled The Ages of American Law.

On the surface, Gilmore's book offers little specific guidance as to how man's laws should govern the clone. It is an analysis of the role of the Federal government in establishing uniformity. From the time of the conversion of the colonies <sup>a</sup> to a republic, the Supreme Court of the United States has discovered and exploited various methods of establishing Federal supremacy-- and thus national uniformity. One method has been to give expansive reading to the powers conferred by the Constitution on the Federal governments and the Federal courts.

The doctrine of Swift vs. Tyson, a case decided in 1842, was that the Federal courts would exercise an independent judgment-- that is, would not be bound by the law of any state. A hundred years later, in the 1938 decision of Erie vs. Tompkins, another Supreme Court declared that the Federal law doctrine of Swift vs. Tyson was, and always had been, unconstitutional. But, having scrapped the Swift vs. Tyson device as a machine that no longer worked, the Court immediately set about providing a substitute Federalizing or nationalizing principle. According to Gilmore, this Federalizing principle is that the presence of any kind of Federal interest in a case is enough to support the conclusion that decision should be governed by Federal law rather than by the law of any state.



One trained in the law will find such swapping of principles a matter of course. One trained in science will find it a marvel of hubris and mortal fallibility. Just as a verdict in the Scopes case could not prove or disprove the origin of species, so will the matter of jurisdiction not determine the safety or harmfulness of genetic research. I suspect, however, that someday--perhaps a number of times--this aspect of Federalism will be crucial in setting the pace and temporarily protecting the right of pursuit of one scientific truth or another. I do believe that now--in contrast to what I believed a year ago--that this aspect of Federalism is the more important in the future conduct of recombinant DNA research.

Of more immediate concern is how the Federal administrative powers shall be used further to govern recombinant DNA research. And here and there in the text and in the generous footnotes of The Ages of American Law, one is led toward unexpected sources of enlightenment. Gilmore, like many legal scholars, is fascinated by the lofty and confusing philosophy of Oliver Wendell Holmes. And any pursuit of its meaning and origins criss-crosses traces of the influence of a Yankee contemporary of Holmes, America's most important philosopher of science, Charles Sanders Peirce. Here are two giants, quirky and obscurantist by turns, who had a deep understanding of, and sympathy for, the scientific method; Holmes did so through patrimony, Peirce as a life-long practicing scientist. Some of the things they had to say about science seem to me to contribute much, if unintentionally, to the question of how far the Federal--or



any government--should go in trying to control the risks in a form of scientific investigation.

Charles Peirce, almost unknown in his own lifetime, has since his death acquired a considerable vogue among philosophers. Like the name of a better-known purveyor of sustenance from the Northeast (S. S. Peirce), the name is pronounced "purse."

Peirce held strikingly original views both about the nature of scientific inquiry and about the nature of knowledge. He regards science as a living thing in an incessant state of metabolism and growth. As a living process, science requires constant scrutiny, evaluation, and self-criticism. As Richard J. Bernstein, editor of a volume of critical essays on Peirce, points out, self-criticism was to Peirce "the very life of reasoning." But it cannot take place in a vacuum; what is essential for self-criticism is an active community of inquirers. It is this body that is ultimately the basis for distinguishing the real from the unreal, and the true from the false. The concept of self-regulation is of key importance in Peirce's philosophic scheme.

Peirce emphasized that science is primarily an activity, a process of inquiry, and only secondarily a systematic body of results. Thus science, as he saw it, constitutes an overt attack by multiple investigators on a particular problem. Of cardinal importance in this community effort is continuing communication, comparison, and criticism of results. Thus,

the work of science is not achieved by any person or single group of individuals, but by the cooperation of many individuals and groups.

It strikes me that Peirce's descriptions of the community of inquirers apply extraordinarily well to the many, scattered scientists working in molecular biology. Theirs is a rapidly moving field, one of the leading edges of biological science. The work in recombinant DNA research is extremely technical and complex. Although the workers have means of keeping scientifically informed, even they have difficulty in keeping abreast of the newest developments. The communication and self-criticism inherent in any science new become critical here, particularly in determining potential hazards in use of recombinant techniques.

The purpose, the conduct, and the achievement of science all revolve about an axis of norms. There can be no self-control or self-criticism unless there are norms by which we can distinguish the true from the false, the right from the wrong, the correct from the incorrect. All reasoning exists in a logical space created by norms. As Bernstein notes, Peirce came to see this point more and more clearly as his philosophic outlook matured.

It is certain that Peirce's views of knowledge and of the nature of scientific inquiry were known to Holmes. Although the lawyer acknowledged no debt, more than a trace of Peirce is apparent in Holmes' jurisprudential theory of objective norms arisen by agreement among members of a community and are

applied by adjudication as a process of inquiry that will continue indefinitely.

Both Holmes and Peirce recognize the community as the important arbiter of standards. In Peirce's case the relevant community is composed of scientific inquirers; for Holmes it is the group of citizens subject to a body of law.

When the molecular biologists at Asilomar set some prohibitions and initial guidelines for themselves, they acknowledged a momentary loss of the norms. When they asked the NIH to assist in the re-establishing of those norms, and when we accepted, neither party recognized the remarkable dimensions of their contract at the time. The community of inquirers was, for its pains, quickly to lose the opportunity to set the norms for itself. A larger American community, roused by suggestion of possible risks to itself, had no interest in relinquishing all interest in the standards to be set. But there was a complication, as there will be in every future confrontation of this kind between scientists and the rest of society; the community of scientific inquirers is not a subset of the group of citizens subject to a single body of law. The norms of a world-wide scientific community can be tinted with local material, but the base must be everywhere the same.

Peirce's requirement of normative standards clearly cannot be set aside for recombinant DNA research. And it is in the nature of this research that those standards be uniform over as broad an area as can be set. At present the practical boundaries are national ones. And for the United States, the best interest of the smaller and larger communities dictate that the standards should exemplify Federalism to its maximum limit.

Where the limits must be drawn in the exercise of Federal power to compel adherence to the norms is very much another question.

Two years' experience with the NIH Guidelines for Recombinant DNA Research have offered some valuable tutelage in the limits of external (Federal) control of laboratory experimentation. One fundamental lesson is that degree of control must bear some relation to degree of risk. Scientists and their co-workers have long worked with pathogenic organisms, poisonous plants and animals, and hazardous chemicals. The laboratory is not among the more notorious occupational settings for accidents or illness. Damage to community or environment by basic laboratory research is almost unknown.

A second lesson is that an inescapable requirement for effective external regulation is the ability to set realistic and durable standards. Control over the use of radioisotopes, one of the rare examples of Federal regulation of laboratory practices, is not comparable to the use of recombinant DNA



techniques. The risks of using radioisotopes are calculable and mistakes are easily measured. Without a base for the setting of such standards, conventional regulation is difficult at best, and can be preposterous, at worst.

In the case of recombinant DNA technology we are in the midst of a search for the risks, and thus looking for the applicable standards. The scientists who raised the possibility did so for the purpose of enhancing the collective nature of the scientific process as Peirce so eloquently described. The usual communication network had to be strengthened and the criticism, comparisons and reaching of consensus greatly accelerated. These actions, it was reasoned, would help establish a set of initial norms for proceeding. There was the added assumption, of course, that what Peirce calls the continued dialogue would keep the norms constantly up-to-date. All scientists using the new techniques would agree that, until things became clearer, each would execute a "memorandum of understanding" that signified complete submergence of self-interest to the objective and universal.

The power to require such discipline of its grantees was an attractive reason for the scientists to have requested Federal intervention. The Federal capacity to achieve the essential enhancement of communications and to maintain the dialectic has been one of the most positive aspects of this experiment in administration.

But the price of Federal administrative practice is high. Its invocation by one group always involves a mixing with the interests of other communities. The normative processes of the scientists ideally will follow the empirical method to a logical conception of reality; the normative processes of other communities may emphasize more subjective values. It has been pointed out that, in his theory of reality in which the ultimate truth comes from scientific alone, Peirce neglected other dimensions in the real truth about things. Should there be a real risk in public safety in what scientists want to do, the public conception of reality, whether entirely logical or not, must prevail.

When the risks to public safety are only hypothetical, an appropriate balance between substance and form is more difficult to maintain. In the absence of norms, discretionary powers are reluctantly given and gingerly assumed. The result may be inflexibility and excesses in central bureaucratic control. It is clear that both kinds of errors have been made in the original Guidelines.

Since concerns were first raised about possible hazards of laboratory experiments with recombinant DNA, thousands of individual applications of such techniques have produced much useful knowledge. No evidence has come to light of a product created by these techniques that has been harmful to man or the environment.

Although it is time to revise the original NIH Guidelines for Recombinant DNA Research, it is not the time to prepare for their early abandonment. Understanding of gene regulation and expression is increasing inexorably and at an awesome pace. Ways will be found to achieve and control the translation of foreign genes by a variety of hosts. As the barriers to translation are dropped, some of the larger promise of recombinant technology will be harvested. In some proportion to the harvest of positive results, there will also have to be maintained a capability for observing any capacity of these experiments to yield harmful products. The communication and the criticism must continue.

In preparation for this next phase of recombinant DNA research, several shifts in emphasis of the Guidelines are necessary. Peirce's argument merits reinforcement. The norms imposed on this kind of activity derive their validity from continual changes dictated by results of the experimentation they guide. The limit of Federalism--as expressed in the universality of the norms--is justifiably extended. The limit of Federalism--as expressed in central administrative practice--recedes as the risks diminish. Experiments posing no threat to safety must be exempted from the Guidelines and provisions made to remove others as soon as their harmlessness becomes evident.

Primary responsibility for compliance with the rules will be shifted more and more to where the work is going on; and there it will be shared fully by the scientists and their peers who must include some who are not affiliated with the institution. The organs of NIH shall be rededicated to central functions, serving the continuing synthesis and interpretation of the Guidelines and the maintenance of full communication among all who must use them.

In effect, there is some limit to the need and usefulness of Federalism in control of scientific process. The entire basis for any Federal intervention to set standards or implement regulations is the potential hazard posed by the research. As this threat diminishes so much the need for Federal intervention.

Public policy in this area may benefit from expression of two other thoughts of Holmes. One relates to an excessive shift of liability upon scientists for engaging in the scientific process. To quote Holmes:

"A man need not, it is true, do this or that act--the term act implies a choice--but he must act somehow. Furthermore, the public generally profits by individual activity. As action cannot be avoided, and tends to the public good, there is obviously no policy in throwing the hazard of what is at once desirable and inevitable upon the actor."



The concept of Federalism and its limits will continue to be debated in each generation. And the debate surely will grow on how far the Federal government should go to protect the public from risks--real or perceived. A balance must be struck on how much Federal law and regulation is enough.

And this brings me to the last use of the words of Holmes to express something of my own sentiment in this prolonged and trying affair. Gilmore concludes his book by paraphrasing Holmes, to wit:

"Law reflects but in no sense determines the moral worth of a society. The values of a reasonably just society will reflect themselves in a reasonably just law. The better the society, the less law there will be. In Heaven there will be no law, and the lion will lie down with the lamb. The values of an unjust society will reflect themselves in an unjust law. The worse the society, the more law there will be. In Hell there will be nothing but law, and due process will be meticulously observed."



DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
PUBLIC HEALTH SERVICE  
NATIONAL INSTITUTES OF HEALTH  
BETHESDA, MARYLAND 20014

STATEMENT BY

DONALD S. FREDRICKSON, M.D.

DIRECTOR, NATIONAL INSTITUTES OF HEALTH

ON

NUTRITION RESEARCH

BEFORE

THE SUBCOMMITTEE ON NUTRITION

COMMITTEE ON AGRICULTURE, NUTRITION, AND FORESTRY

UNITED STATES SENATE

June 13, 1978

Mr. Chairman and Members of the Subcommittee:

I welcome the opportunity to renew with you today our discussions on nutrition research at the National Institutes of Health. I believe it is fair to say that this area of research is achieving greater visibility, a higher priority, and better recognition. I would add that this Committee's activities have contributed much to the increased stature now accorded nutrition research.

You will recall that at the hearing last October the flow of discussion tended to break down over perennially difficult problems of definitions. The overall level of nutrition research reported by the NIH was questioned, as were the kinds of research projects included within that total. I regret, on that earlier occasion, we could not agree on the validity of all the results or analyses of nutrition research. And, indeed, as we have worked further to clarify and refine reporting, the difficulties have not disappeared. Nevertheless, our reassessments and analyses have been made, and we stand ready to report once again on NIH nutrition research.

First, a word about process: After our testimony last year, we did two things. First, we further refined our definition of human nutrition research. Second, we asked each Institute to re-examine its own activities based on that definition. To do this, each Institute reviewed all research projects in order to identify the nutrition component and the associated funds. We felt that this process would provide a more accurate assessment of our support for nutrition research than when we assign all of a given project to one of three categories:

those "primarily" devoted to nutrition research, those "secondarily" devoted to nutrition research, or those only "related" to nutrition to a lesser degree. Because the titles of some projects may not reflect the nutrition component, each Institute was asked to supply an explanation or justification for those projects whose relationship to nutrition was not revealed in its summary description.

It has been a long and tedious process, but I believe that the cumulative level of funding derived from our analysis is an accurate assessment of our activities. Our calculation of the amount that NIH obligated in fiscal year 1977 for nutrition research was \$93,346,000. This total includes research grants, contracts, clinical trials, centers, intramural research, international nutrition research, and training. Of that, \$9.5 million was spent for clinical trials which have direct implications for dietary prescription in humans, an area in which you have expressed interest. In another area of interest to you, nutrition and prevention of disease, NIH spent \$37.7 million. This latter figure includes research in such areas as obesity, hypertension, cancer, diabetes, etc.

The Office of Science and Technology Policy has recommended the following nutrition research priorities: Effects of Nutrition on Human Health and Performance; Food Sciences; Nutrition Education Research; and Diet and Nutrition-Related Health Status Surveillance. If we use these as a base, NIH spent a total of \$69.3 million in fiscal year 1977. The remaining \$24 million (based on the NIH total) was expended for nutrition education, intramural research, all types of training, and international nutrition research.



A new coding system, developed by the Division of Research Grants, and a classification system being developed by the Nutrition Coordinating Committee, will enable the Institutes to retrieve readily information regarding the nutritional components of all projects. Retrieval of such information heretofore had to be undertaken by reviewing each project, such as the process we have gone through to provide the figures I have just cited.

I'd now like to discuss some other activities which have occurred since last year.

The Nutrition Coordinating Committee has been very active. I am personally involved in many of its activities and meet regularly with its chairman and vice-chairman to keep apprised of its activities. I am especially pleased with the program of the national conference it is sponsoring on June 19 and 20 at NIH, entitled "The Biomedical and Behavioral Basis of Clinical Nutrition: A Projection for the 1980's." Most of the leaders in nutrition research in this country will be involved in reviewing biomedical and behavioral research in nutrition, and relating this research to current clinical practice, and projecting the future frontiers of nutritional investigations. Participants on the various panels include consumers, Congressional staff, and the scientific community. A press release has been circulated widely and it is expected that the public media and professional journals will be well represented.

It was also through a subcommittee of the Nutrition Coordinating Committee that a review was undertaken of NIH nutrition publications intended for lay audiences. Based on the subcommittee review, 60 percent of the publications, while satisfactory in some respects, were

found to be deficient in other respects and were recommended for withdrawal or revision. Later this year, publications written for professional audiences will also be reviewed by the subcommittee and consultants, as appropriate. In the near future, it will also develop a set of recommendations for future publications on nutrition. All revised or new NIH publications on nutrition are now being submitted to the Nutrition Coordinating Committee for review and concurrence.

We have mounted a number of specific programmatic efforts since our appearance last year. I was pleased with the response to the National Institute of Child Health and Human Development (NICHD) Request for Application (RFA) on infant nutrition. That Institute received 200 letters of intent by the end of January and 80 applications by the beginning of March. These applications are now being reviewed and will be considered by the NICHD Advisory Council in October. The NICHD is augmenting its research support in infant nutrition, including research on the composition of breast milk, clinical trials on the use of human breast milk for treatment of premature and low birth weight infants, various subcomponents in nutritional disorders of infancy, and comparisons of compositions of breast milk and various formulae.

The NICHD is also planning to support research on the development of dietary habits and on techniques to improve dietary habits that are detrimental to health. This research will be stimulated in part through a recently issued RFA entitled, "Health Promotion and Prevention of Smoking and Other Behaviors Detrimental to Health." A major portion of research on food habits, however, is expected to evolve from the NICHD Program on Clinical Nutrition and Early Development which is

now under way. This new program will extend the Institute's current biomedical effort in nutrition research into behavioral, social, and cultural influences on nutrition, as these relate to the promotion of health and prevention of disease. An important aspect of the new program will be the study of food habits and food avoidances during pregnancy and lactation in order to optimize the health of the mother and her infant.

The National Institute on Aging (NIA) has begun its program in clinical nutrition. NIA's RFA in clinical nutrition for the aged precipitated more than 300 inquiries. Grant applications resulting from the RFA will be reviewed in October. To assist the NIA in developing its program in clinical nutrition, the Institute sponsored, on June 6, 7 and 8, a major conference entitled, "Nutritional Needs and the Health of the Aging Adult." The experts in nutrition and the aging will be providing the Institute with a set of recommendations which will reflect the best thinking on this subject.

Negotiations are proceeding between NIA and the National Center for Health Statistics (NCHS) to study the effects of nutrition on the elderly. Procedures are being worked out to follow up cohorts which were examined in previous NCHS nutrition surveys.

In addition to research which NIH supports, we have established the Office of Medical Applications of Research to seek consensus in the biomedical research community with involvement or in concert with others, as appropriate, new and existing technologies to assure that these technologies have been validated for safety and efficacy. Critical to this process is the translation and dissemination of such information emerging from these exercises in a way that is acceptable

to the practicing community and to others who need to know. As part of that office's activities related to nutrition, a consensus development conference will be sponsored on December 4-5, 1978, by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) on "The Surgical Treatment for Morbid Obesity." Included in their review will be the appropriate use of intestinal by-pass surgery and types of surgery, short- and long-term effectiveness of each surgical procedure, subsequent mortality and morbidity data, untoward side effects, and possible end results.

Another consensus development conference is also planned to develop recommendations on the subject of total parenteral nutrition and hyperalimentation, therapeutic measures of great interest and some controversy at present.

Finally, the Nutrition Coordinating Committee is in the process of developing a joint program announcement on obesity. Several Institutes with mutual interests in obesity will be soliciting grant applications for the support of research in the biomedical and behavioral aspects of exogenous obesity.

The NIH also is participating in the DHEW Nutrition Coordinating Committee, which has met regularly since March. The Committee is beginning regular interdepartmental meetings with the Department of Agriculture. These meetings, in which NIH representatives will be directly involved, will provide an opportunity for joint consideration of a broad range of issues in nutrition of concern in both Departments. We view this as a critical first step in remedying the lack of close interaction between DHEW and USDA, which has existed far too long.



In addition, the Deputy Assistant Secretary for Health (Special Health Initiatives), the Commissioner, Food and Drug Administration, and I met with Ms. Carol Foreman, Assistant Secretary for Food and Consumer Services, USDA, and Dr. Rupert Cutler, Assistant Secretary for Conservation, Research, and Education, USDA, to discuss national dietary goals. As a follow-up to this meeting, an interdepartmental working group is being formed to further explore this issue.

In summary, Mr. Chairman, we are continuing to increase our emphasis on nutrition research and education at the NIH within the limits of available resources. Nutrition clearly is a high priority area mission at NIH. We recognize that more needs to be done and, that to do this, there must be sufficient trained people to undertake the research. I know you are interested in present activities of the NIH, as well as future plans. I'd like to briefly outline two areas which will receive emphasis.

First, we are exploring the establishment of Clinical Nutrition Research Units, both within the Clinical Center at NIH and in institutions across the country. The Units would provide a central focus for clinical human nutrition research and training in one or more specific clinical or basic science areas that will enhance the opportunities for clinical research experience and training of medical personnel in nutrition. We expect the units to stimulate the development of improved methodologies and systems of assessment of nutritional status and treatment of patients in order to encourage the application of appropriate measures in nutritional health care, particularly of the hypermetabolic patients, and to increase efforts to provide nutrition education to patients of all sorts.

The second area of emphasis will be in training. At the moment, we are training 205 persons in nutrition-related fields. We need to do more. I hope next year to report to you on our progress.

This concludes my prepared statement. I shall be happy to answer any questions you or the other subcommittee members may have.

## OPENING REMARKS\*

by

Donald S. Fredrickson, M.D.\*\*

I want to extend a warm welcome to all of you and to thank the program participants for their contribution to this Conference.

I believe this is the first time that scientists, Congressional staff, consumers, and government officials have appeared together in a program to discuss the "Biomedical and Behavioral Basis of Clinical Nutrition" -- along with an audience representing nearly all walks of life in our society.

We at the National Institutes of Health are particularly pleased that the Food and Drug Administration (another agency of the Public Health Service within the Department of Health, Education, and Welfare) and the Department of Agriculture (another department where both human nutrition and food sciences are given special attention) will be presenting their programs in nutrition research along with us.

You might be interested in learning about the history of nutrition research at the NIH:

During the last decade, support for nutrition research at NIH has more than doubled; however, for the outset nutrition has influenced the total scope of NIH biomedical research. As each Institute and Division has added nutrition programs to

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\* Presented at "The Biomedical and Behavioral Basis of Clinical Nutrition: A Projection for the 1980's" -- Nutrition Conference June 19, 1978, Building 10, Masur Auditorium, N.I.H.

\*\* Director, National Institutes of Health

its growing responsibilities, the overall nutrition effort at NIH has broadened.

In early 1900's, a comprehensive study of nutrition as it relates to disease prevention was initiated by Dr. Joseph Goldberger (the discoverer of pellagra as a nutrition-deficiency disease) at the Hygienic Laboratory of the Public Health Service. The Hygienic Laboratory was redesignated as the National Institutes of Health by the Ransdel Act of 1930.

In 1947, the "Sebrell" Laboratories of Nutrition, Chemistry, and Pathology, by then located in Bethesda, were incorporated under the Experimental Biology and Medicine Institute. In 1950, both the Institute and the laboratories were authorized by the Omnibus Medical Research Act to become the National Institute of Arthritis and Metabolic Diseases. In 1953, the Laboratories of Nutrition, Chemistry, and Pathology became the Laboratory of Nutrition and Biochemistry.

Although the current nature of intramural nutrition research in the Public Health Service is considerably different from that initiated by Drs. Goldberger and Sebrell, the Laboratory of Nutrition and Endocrinology remains today as a research facility within the National Institute of Arthritis, Metabolism, and Digestive Diseases. This laboratory is the direct descendant of the original U.S. Public Health Service Corps laboratories of the period from 1914-38.

Between 1959 and 1960 "classical nutrition" was de-emphasized in NIAMDD, reflecting a movement around the world, taking nutrition



into more basic laboratory pursuits. Now nutrition research is conducted by every Institute with two major new programs in clinical nutrition initiated during the past year in NICHD and NIA. Although the amounts involved have been a tug-of-war, today NIH conducts or supports the largest share of clinical nutrition research in the United States. Nutrition research is an area for which the agency is especially qualified to play a leading role because of the amalgam of biology and clinical medicine that is represented. Nutrition has always occupied an important place on our list of research priorities. The current annual expenditures in this area are in excess of \$90 million, and the NIH research programs range from nutrition in pregnant women and infants to nutrition for the aging. The research is concerned with nutrition as a means of preserving health and as a means of combatting disease.

Nutrition is a priority area in the Public Health Service. It is indeed a pleasure for me to present to you Dr. Julius Richmond, Assistant Secretary for Health and the Surgeon General of the Public Health Service.

INTRODUCTION FOR RENE DUBOS:

We are honored today to have with us one of the world's most distinguished scientists. His work in nutrition and infection, in the effects of environmental forces on human life, in cellulose decomposition, in bacterial cultures, and in bacterial enzymes has laid the foundation for remarkable scientific achievements.

These achievements have been noted by the numerous professional societies of which he is a member. He has received awards, for example, from the American College of Physicians, the National Tuberculosis Association, and the American Clinical and Climatology Association, as well as the Pulitzer Prize and the Phi Beta Kappa award. He is also a member of the National Academy of Sciences and the American Philosophical Society.

In addition, he has received 25 honorary degrees from universities in the United States and around the world.

He now carries the distinguished title of Professor Emeritus of Rockefeller University, where he has been associated for over 50 years.

Ladies and gentlemen, Dr. René Dubos.

Introductory Remarks for the Honorable George McGovern

LADIES AND GENTLEMEN:

South Dakota is well known for several reasons --

- For the famous Mount Rushmore, where the faces of Washington, Jefferson, Lincoln, and Theodore Roosevelt are carved in granite twice the height of the Great Sphinx of Egypt.
- South Dakota leads the Nation in gold production with the largest gold mine in the Western Hemisphere.
- It has the largest herd of bison (buffalo) in the world.
- Perhaps a little known fact is that Butte County, South Dakota is the geographic center of the United States (including Alaska and Hawaii).
- South Dakota is also known for its famous sons-- most notable, Sitting Bull, Crazy Horse, and Ernest O. Lawrence, the physicist who is credited with one of the great tools of biomedical research-- radioactive isotopes.

South Dakota is also the home of our first speaker this morning. He was born in Avon, South Dakota, grew up there and in Mitchell, South Dakota. He originally contemplated a career as a minister. He attended Wesleyan University and received his Ph.D. from Northwestern University. Prior to his political career, he

taught history and political science at Dakota Wesleyan. He served in the Army Air Force, flew about 35 combat missions and won the Distinguished Flying Cross. His career history as a politician is familiar to all--candidate for the Presidency in 1972, Chairman of the Senate Select Committee on Nutrition and Human Needs for ten years.

This Committee was responsible for the publication "Dietary Goals for the United States." The Report has had an important impact on the scientific community, as well as the people of the Nation. It certainly raised the level of consciousness of HEW and has contributed much to the increased stature now accorded nutrition research.

The activities of the Senate Select Committee have been assumed by the Nutrition Subcommittee of the Senate Agriculture Committee. I am pleased and honored to present its Chairman, Senator George McGovern.



## THE MacNEIL/LEHRER REPORT

Air Date: June 19, 1978

## Transcript of "War on Cancer"

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ROBERT MacNEIL: Good evening. For the first time, last week, an issue that has been as sacrosanct to politicians as motherhood came under major attack in the Congress: it's the so-called war on cancer. Led by a conservative Republican and a liberal Democrat, Senators challenged the way the government is spending almost a billion dollars a year looking for a cancer cure. Their criticism brought to a head questions individual scientists and others have raised since the program was voted seven years ago: principally, whether throwing billions of dollars into a crash program is the right way to approach a set of diseases as complex as cancer. Tonight, was the war on cancer a bad idea in the first place, or a good idea with problems? And what should be done about it now? Jim?

JIM LEHRER: Robin, critics have begun to refer to the war on cancer as a kind of medical Vietnam; seven years and five billion dollars after the war was declared, there is not only no victory but not even a light at the end of the tunnel. It's a project with an interesting political history. A liberal Democratic Senator from Texas, Ralph Yarborough, first proposed a major governmental commitment to finding a cure for cancer more than ten years ago. President Nixon picked up the idea in 1971. He announced it in his State of the Union message that year, saying that "the same kind of concentrated effort that split the atom and took man to the moon should be conquering this dread disease." He expressed the hope that a cure for cancer could be found by the 1976 bicentennial year. It hasn't happened. Cancer still ranks behind heart disease as the number two killer of Americans, more than 350,000 a year. Now many people, as Robin said, particularly in Congress, are asking about how that five billion dollars has been spent these last seven years, and foremost among those asking the questions is Senator Robert Dole, Republican of Kansas and ranking minority member of the Senate Agriculture Committee subcommittee on nutrition, which held those hearings last week.

Senator, what is your assessment of the war on cancer after seven years and five billion dollars?

Sen. ROBERT DOLE: Well, I think it's fair to say that many of us in Congress, at least, think we may have failed; somewhere along the line we've concentrated on appropriations, very little oversight, very little investigation on our own. We just appropriate more money because we think that may be the way to fill in the blanks in the Conquest of Cancer Act, and I think we're disappointed. We're not faulting anyone in particular; we think there ought to be more emphasis in certain areas. I think we've come to realize that just pumping money into the program itself hasn't yielded many results.

LEHRER: Have there been any results that have come to your attention as a result of this?

DOLE: Oh, I'm certain there are a number of things, and I'm certain Dr. Fredrickson will comment on some, but we've been focusing primarily

on nutrition. When you see that about forty percent of cancers in men and sixty percent of cancers in women are nutrition-related, we don't understand why they're spending only one percent of their budget on nutrition prevention. And we're talking about billions and billions of dollars; just this past week the Senate Appropriations Committee said, "We're going to give you \$867 million in fiscal '79," it's going to \$950 million in fiscal 1980; that's almost a billion dollars a year. And we just believe the American people would like some response.

LEHRER: Who do you think should make the decision on how that \$950 million should be spent?

DOLE: Well, of course the National Cancer Institute and of course Dr. Fredrickson, who has overall control -- I don't quarrel with their right to make the decision. But we believe there should be more emphasis, and we don't buy the argument that, well, there's not enough professionals around the nutrition field. I suggest if we tell the American people, as we did in the space program, a step forward, we have money available to see if we can't find some ways for prevention. And that's our one objection; we want to cure cancer, certainly. Everyone does. But what about prevention in the meantime? What are we doing in that field? We're not doing enough.

LEHRER: Is that your overall criticism, that too much emphasis has been put on finding a cure rather than preventing it?

DOLE: Right. We don't believe there's been much at all as far as nutrition prevention, when you're talking about \$12 million dollars is all we're spending on nutrition prevention in a budget of hundreds and hundreds of millions of dollars. And this is after some pressure from the Congress last year, after some pressure from the Congress in 1974; and again, I don't want to quarrel with those who have control of the program, I just want to focus on what we think would be a proper emphasis.

LEHRER: Senator, in political terms -- as Robin said at the beginning this is the first time that the war on cancer as such has been attacked because it's been kind of hands-off politically -- you, a conservative Republican and George McGovern, a liberal Democrat, have suddenly sounded the clarion call. What does that mean politically? Has there been a change, or what?

DOLE: I think it means that maybe we haven't done enough in the past. You know, I think we overstated -- I haven't checked the record, but I probably made a statement back in '71 about the conquest of cancer; many members of Congress did; they were totally sincere, they were properly motivated -- I think we overstated the case as far as finding a cure for cancer in one year, two years, maybe a decade, maybe even longer. So now we're sort of sitting back -- hindsight's always very good -- saying, "Look, we've spent all this money and nothing's happened, or not enough has happened, or not the right things have happened." And I think we understand that the taxpayers are beginning to put pressure on us all over the country -- California; Washington, D.C. -- what are you getting for your money? And we, I think, in turn, are asking those questions of Dr. Fredrickson and others who have the responsibility. I'm permitted to say that maybe we shouldn't spend any more money, unless we rearrange our priorities.

LEHRER: Just stop it.



DOLE: Well, in other words, not increase the budget; continue what we're doing, but not annually have this budget increase just because the word "cancer" is involved if we determine as a legislative body that the priorities are not correct.

LEHRER: All right; thank you. Robin?

MacNEIL: In the scientific community one criticism of the war on cancer has been that it's placed too much emphasis on the search for a virus or viruses that might cause it, and too little on environmental factors. Dr. Irving Selikoff of the Mt. Sinai School of Medicine in New York is one of the leading experts on environmental causes of cancer. He's served as a consultant to the American Cancer Society. Dr. Selikoff, do we need to reorder the priorities in the so-called war on cancer?

Dr. IRVING SELIKOFF: I'm sure we do. I think we always have to reorder our priorities; probably year after year, as new things come about, new opportunities are found, I think that means that we have to see what we should now do. And I'm delighted to hear Senator Dole and others in Congress questioning us, prodding us precisely to do this. Senator Kennedy and Javits and Senator Williams and Congressman Obey and Congressman Andy Maguire and Paul Rogers and so forth -- they have been prodding and they have been questioning, and I'm delighted to hear what Senator Dole is now doing, and Senator McGovern. This is good. We have to take advantage of new opportunities, and many of these opportunities now are in the environment.

MacNEIL: Well, is it just a question of now taking advantage of opportunities that have presented themselves, or was the program misdirected, in a sense, from the beginning? First of all, was it a sort of silly idea? Was the state of knowledge such that it was a good idea to declare a war on cancer in a crash program?

SELIKOFF: Well, I expect that the term "declaring war" is a political term. I don't think scientists ever felt that way about it. And it wasn't a silly idea; there were a hundred scientists that were sequestered out in the country to come up with what they thought were the best leads and best opportunities, and the plan was put together that way. Now, since research is always in the future and always unknowable -- you never know what's going to happen -- you've got to guess wrong sometimes. We hope that we'll guess wrong as little as possible.

MacNEIL: Where the program is at the moment, are we guessing wrong in directing too much of the research money into one area and not another?

SELIKOFF: Sure.

MacNEIL: Into which area, and which area are we neglecting?

SELIKOFF: The areas in which we're doing research now were set five, six, ten years ago, and it represented the best ideas of that time. I'm sure the best ideas now would be somewhat different. So without even knowing what is being done, I'm sure all of us could say it could be improved upon. The improvement at the moment looks as if it will be things outside of us. We're beginning to learn the causes of cancer. This is a remarkable time in human history. It's only in the last twenty years that this has begun to happen. It started with the great American Cancer Society study concerning lung cancer. When we found that the most common cause of cancer in men, lung cancer -- this year it's going to

take some 80,000 lives -- was due to something outside of us, not programmed into our genes, well, that taught all of us a lesson: that things that cause cancer, by and large, are outside of us. And that's where we're looking now.

MacNEIL: Senator Dole said a moment ago, we've looked at all this expenditure and we see nothing has happened, or very little has happened. Has something happened in the war on cancer? Has it been productive?

SELIKOFF: Oh, a great deal has been done. We've learned more about what's happening in the cells, in the proteins, the basic mechanisms -- it hasn't paid off yet, but this is where it's likely that we will find much payoff. We've found that treatment of certain cancers is very much better; nowhere near what we would like, but just ten, fifteen years ago I know in the hospital when a patient had the diagnosis of Hodgkin's disease it was almost a death warrant. Now almost fifty percent can be kept alive. You say, well, that's not enough; we're not curing enough lung cancers. Yes, that's true. But treatment is very, very important. We are not going to get the last thirty-five years back; we're not going to stop people from smoking once they've got the habit, in large part. Therefore, we've got to learn how to treat the results of our inadequacies of the past. So treatment remains very important. To find out what's causing cancer is additionally important. It's not either/or; we have to do both. Now, you mentioned that Senator Dole is a conservative Republican and Senator McGovern is a liberal Democrat; true. But when it comes to cancer there are no Republicans and there are no Democrats. I think we all are in this together. And here this can be translated, we have to have the treatment, we have to have the research into the basic mechanism to understand what's going on, and we also have to find what's causing cancer so that we can prevent people in the future from being exposed to these things.

MacNEIL: Thank you. Jim?

LEHRER: The agency in overall charge of dispensing and administering federal money for cancer research is the National Institutes of Health, and Dr. Donald Fredrickson, the man that Senator Dole mentioned a moment ago and who was a witness before Senator Dole's subcommittee last week, is Director of NIH. First, Dr. Fredrickson, is Senator Dole correct in questioning the results of the war on cancer thus far? Is he justified?

Dr. DONALD FREDRICKSON: Well, I think he is, in the sense that the public is the patron of research in this country and I think that we welcome that kind of creative tension, that constant exploration of whether we've actually embarked upon the right course to achieve what the public expects from science as it's supported in that way.

LEHRER: Seven years ago was the wrong course embarked upon?

FREDRICKSON: Well, yes and no. I think that a great many scientists then could tell you that now they knew that road was far longer than many felt it was, that one could not expect then a quick cure, that we were going like a trip to the moon; it was a very different kind of shot, a far longer shot, and it will take many years and a great deal of investment.

LEHRER: But yet, Doctor, I recall seven years ago when that was announced, that the scientists were very quiet with their reservations, for the simple reason that they wanted the big bucks that were going to



go with the research. Why didn't they speak up then?

FREDRICKSON: Well, some did. But of course, many others felt that actually all you had to do was to make that giant step in investment and that the course could be accelerated. I think that both sides were genuine in, on the one hand, their reluctance to commit to a goal and, on the other, their genuine enthusiasm.

LEHRER: All right, to the specific that Senator Dole mentioned, which is that one percent of the funds are being expended now for research on nutrition, and there's already been scientific research that indicates there is a connection between what we eat and cancer. Why is that?

FREDRICKSON: Well, I think that the amount going into the field of nutrition in cancer research does appear to be low relative to some of the facts that have been discovered by some of that same money, but also money which has been attributed to studies of epidemiology, looking for the occurrence of cancer in different populations in different parts of the world. I think we're just at the...

LEHRER: What does that mean?

FREDRICKSON: Well, the study of how cancer differs in incidence in different populations has led also to a study of what may be the differences in those populations. And at the moment...

LEHRER: In other words, a genetic difference, or a racial difference or an environmental difference, depending on where you live?

FREDRICKSON: That's one of the things one looks at first, when you see differences in different parts of the world. But I think that we can rule out genetic factors as being the key ones; clearly they are more likely to be environmental. And among those there are cultural differences, and perhaps the most important of these do appear to be what people are eating. The one problem is here, and that's where we are at the present stage, that an association of a different kind of diet with a different incidence of disease still doesn't mean that that is a direct cause. When one population group, one culture, changes diet it also changes a great many things. The air that it breathes usually changes, the physical activity -- a whole variety of other things, including other cancer-causing agents and their exposure to them, also undergo change. And we're now at the stage of just embarking on a separation of those first suggestions, that diet indeed must have some close relationship to the difference in incidence of cancer in many different people.

LEHRER: Doctor, after seven years and five billion dollars, are we any closer to finding a cure for cancer?

FREDRICKSON: I would have to say that we almost certainly are. But those differences are, like Dr. Selikoff stressed, primarily in our understanding of the cell. When we understand the cell, we'll understand why it goes wild and becomes what is called cancerous. And it is in this way, understanding those humoral mechanisms that determine the way cells grow together, what makes them grow normally and kept under the body control and suddenly leap it, where we've made the greatest advance. I think...

LEHRER: Significant advance as a result of this program?

FREDRICKSON: I think without any question that much of the money that's been spent in the cancer program today has been a major factor in this extraordinary explosion of knowledge about cell biology and what controls the growth and the functioning of the cell. This, after all, is going to be the place where the keys to the many kinds of cancers that we have are ultimately found.

LEHRER: All right; thank you. Robin?

MacNEIL: Senator Dole, I kind of hear some of your answer to the question you've been asking, from these two scientists; that while there may not have been the great breakthrough and the great sort of cure that they can put a signboard on and call it a victory, that actually they've made very, very steady progress in the basic knowledge that they're acquiring about cancer. What do you think about that?

DOLE: Well, I think the point that's hard for us to understand, maybe as legislators and not professionals, as the other two gentlemen are: we look at figures saying that fifty percent of cancers are diet-related, and then we look at the figures on what we are spending to find out about the diet-and-cancer relationship and we find one percent or less. And that's only come about after a lot of prodding by the Congress. And again, I don't want to quarrel with either gentleman on the program, but it just seems that if that's a fact, if sixty percent in women and forty percent in men are sort of somehow diet-related and fifty percent of all cancer is diet-related, why are we spending only one percent on prevention? We spent eighty percent of the money looking for a cure, when I think a greatly higher percentage than that can be prevented. And we just believe the priorities are not properly placed.

MacNEIL: Senator, could I just play devil's advocate for a moment and ask you: if in the beginning, seven years ago, politicians and scientists were quick to minimize the length of the time that might be necessary and to make it perhaps a bit oversimplistic, are you in the Congress not falling victim to that same tendency to say, "Hey, where's the breakthrough and where's the result," when in fact there has been a great deal of very worthwhile work done up till now?

DOLE: I don't want to suggest or leave the implication that it's been money down the drain. I want to leave the impression that we believe that within that five billion or six billion dollars more should have been spent on nutrition research and how it might prevent cancer, if really we have fifty percent connection. If we go back to '74, '75 and '76 we think there's a little more progress, but it's very slow.

MacNEIL: Let's put that to Dr. Selikoff. Is the nutrition area one part of the potential environmental causes of cancer which would be fruitful to put a lot more money into and a lot more effort right now?

SELIKOFF: I think we have to look at that possibility. As Dr. Fredrickson pointed out, we're very curious and concerned about the fact, for example, that people in Japan have comparatively little cancer of the colon; people in the United States have a great deal. When Japanese move to the United States, their colon cancer rates tend to go up; in fact, their first-born in this country have the same high colon cancer rates as all other Americans. Now, one of the possibilities, obviously, is, is it something in the diet?

MacNEIL: Something we eat and the Japanese don't, or we eat more



of than they do, or something.

SELIKOFF: Yes; that's a possibility. Nobody really knows the causes of colon cancer or breast cancer or pancreatic cancer or ovary cancer and so forth. Some people think a good deal of it may be in the diet, other people think it may be radiation or cosmic rays, or other people think it's environmental chemicals or that industry is inundating us, and so forth; we don't know.

MacNEIL: All these are equally plausible hypotheses at the moment?

SELIKOFF: Well, those who hold each one tell us that theirs is obviously the best. We're looking for good ideas in these things to test. For example, Dr. Hammond twenty years ago was concerned, at the American Cancer Society, with the question of food; and they registered one million people in 1959 and 1960 and asked them many questions, including what did they eat, did they eat a lot of fried food, did they have fat on their meat and did they eat, let us say, fried fish, and so forth. And now, twenty years later, looking at what happened to that million people, we find that those who ate fried food got cancer and those that didn't eat fried food got cancer, and those who ate cereal got cancer and those that didn't eat cereal got cancer, and those who had a lot of frankfurters got cancer and those that didn't. And we can't sort it out yet. This is a fertile field for research, but it's a tough field.

MacNEIL: If it is a fertile field, Dr. Fredrickson, why is so little spent on it at the moment, relative to the other things? Or are you planning a substantial increase in it?

FREDRICKSON: Well, actually, there is a gradual increase in the amount of research in the area of nutrition, both in general and certainly that related to cancer. I think that it's important for us to sort out here, Senator Dole has given you some figures that I think are not quite what they are today, and that is that about forty-five percent of the total cancer budget is going toward problems that relate to the diagnosis and treatment of cancer. Now today we see a shift toward preventive research and about fifty-five percent of the total effort is going toward mechanisms for finding out the cause and thus the prevention of cancer.

MacNEIL: Well, how did that shift in emphasis come about, Dr. Fredrickson? Is that just something that you chaps sitting at NIH figured would be a good idea, or is it arising out of the reports from the research, or how does that happen?

FREDRICKSON: Well, I think it arises from all those directions. First of all, we try to keep monitoring the research; the scientists themselves are the most accurate monitors of all the activity, and in their own peer review evaluations it is they who tell us what are the most likely results or kinds of explorations that will have the highest payoff. It's a kind of decision that is also made by government administrators, their public advisors; and it certainly is one shared by the Congress, because, as they should, they are one of our closest critics and each year deal intimately with the manner in which these monies are to be distributed against looking for a cure on the one hand and searching for prevention on the other.

MacNEIL: Thank you. Jim?

LEHRER: Dr. Fredrickson, are you willing to let Senator Dole and

the other members of the Congress say, "Okay, we'll give you \$950 million next year, but I want twenty percent of it spent this way, ten percent of it this way, then you go out and spend it. But you either spend it our way or forget it" -- is that all right with you?

FREDRICKSON: Well, I would do my best to try to persuade Senator Dole to not do exactly that but to give us a little more discretion and to believe that we too share his desire to move in the direction of prevention and to take advantage of what seem to be extraordinary opportunities in the information that's now related to nutrition. But it takes time. You've got to have the techniques to properly explore, because the other side of that coin is the danger of wasting the public money, and I know that neither he nor I want that to happen in the pursuit of cancer.

LEHRER: Are you willing to give the scientists full discretion, Senator?

DOLE: Well, we don't quarrel with that, except we would like, as we've written to Senator Magnuson this year, the Senate Appropriations, would he please make \$30 million available for nutrition research. And I think as recently as yesterday Dr. Upton, the head of NCI, indicated that he agreed in essence, that we should spend more in this field.

LEHRER: But that came from the Congress; that's my point. Senator Dole and Senator McGovern are getting that \$30 million spent on nutrition research, right, rather than the scientists.

DOLE: Well, we'd rather do it through some persuasion than earmarking. I think earmarking would be a mistake. We're not scientists; we can't, as legislators, say it ought to be ten percent for this and twenty percent. But we do believe, if we can believe anything that we read -- and we believe a lot of it -- that nutrition is a factor, there should be more money spent on that research, and we hope that through persuasion and committee hearings that we can bring that about.

LEHRER: Well, you mentioned a moment ago, first time around, one element of persuasion that you have, if I read what you said correctly, is that if they don't do this you're not in favor of giving them any more money. That's pretty persuasive, is it not, Doctor?

FREDRICKSON: That's the ultimate persuader, yes.

DOLE: And I say that in a friendly way, not in a hostile way; but it seems to me that we've sort of had perfunctory hearings, we just pass a bill if it's for cancer, whether it's \$500 million, \$600 million; and maybe we should. And I don't fault anybody on the other side; that's our responsibility. Maybe we haven't taken a close enough look ourselves.

LEHRER: Dr. Selikoff, how do you feel about Senators like Dole and others telling you scientists how you ought to spend your money on cancer research? Does that bother you as a professional?

SELIKOFF: Oh, not at all. They may see things or priorities that we might not see. Sometimes we get so tied up with the detail of what we consider is magnificent that we may not see the forest for the trees. And I think that's all good. I don't know about this \$30 million figure for nutrition; I think if there are research projects that have a great deal of promise that might cost \$50 million, we ought to have \$50 mil-



lion, but by the same token, if we only have good research that would cost \$15 million, I think we ought to limit it to \$15 million. I think we need good ideas, good scientists and good work to be done.

LEHRER: Dr. Selikoff, let me ask you another question. Why, seven years ago, when the politicians declared war on cancer, did the professional scientists not come forward publicly and say, "Hey, you're misleading the people if you think that we can come up with a crash program to come up with a cure for cancer"? Was it the need and the desire for research money, as has been charged, or what was the reason? Why was everybody so quiet then?

SELIKOFF: Well, not everybody was quiet, but by and large I think what you say is true. But I also think that it was probably well worthwhile to welcome the support that was then going to become available. And as Dr. Fredrickson has pointed out, much has been done. I don't think that scientists are foolish and that science is bad; I think that a great deal has been done. For example, four years ago we didn't know that vinyl chloride caused cancer of the liver. We hardly knew very much about, let's say, bischloromethyl ether, or for example, only in the last several years did we find out that women who were given diethylstilbestrol during the first trimester of pregnancy later on had babies that got cancer.

LEHRER: Doctor, we have to go.

MacNEIL: Thank you very much, gentlemen in Washington. Good night, Jim. Thank you, Dr. Selikoff. That's all for tonight. In closing we'd just like to welcome viewers of a new Public Television Station which begins carrying this program tonight. It is KOET, Channel 3, in Eufaula, Oklahoma. We'll be back tomorrow night. I'm Robert MacNeil. Good night.

GOVERNMENT PATENT POLICIES: INSTITUTIONAL  
PATENT AGREEMENTS

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HEARINGS  
BEFORE THE  
SUBCOMMITTEE ON  
MONOPOLY AND ANTICOMPETITIVE ACTIVITIES  
OF THE  
SELECT COMMITTEE ON SMALL BUSINESS  
UNITED STATES SENATE  
NINETY-FIFTH CONGRESS  
SECOND SESSION  
ON  
GOVERNMENT PATENT POLICIES

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PART 1

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MAY 22, 23, JUNE 20, 21, AND 26, 1978



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## CONTENTS

### Statement of—

Baruch, Dr. Jordan J., Assistant Secretary of Commerce for Science and Technology, appearing for Dr. Frank Press, the President's Science Adviser.....	Page 975
Bremer, Howard W., patent counsel, Wisconsin Alumni Research Foundation, Madison, Wis.....	373
Cassell, Frank A., assistant chancellor, University of Wisconsin-Milwaukee.....	770
Dunner, Donald R., Esq., attorney at law, on behalf of the American Patent Law Association.....	571
Feerst, Irwin, consulting engineer and member, Committee of Concerned Electrical Engineers, Massapequa Park, N.Y.....	359
Fettig, Hon. Lester A., Administrator, Office of Federal Procurement Policy, Office of Management and Budget.....	985
Fredrickson, Dr. Donald S., Director of the National Institutes of Health.....	782 ✓
Graham, Robert P., Commissioner, Federal Supply Service, General Services Administration, accompanied by Philip G. Read, Director, Federal Procurement Regulations, General Services Administration.....	290
Herz, Charles H., General Counsel, National Science Foundation, accompanied by Jesse Lasken, Assistant to the General Counsel.....	250
Jacobs, Norman A., on behalf of the Licensing Executives Society, Washington, D.C.....	603
Jones, Dr. Thomas F., vice president for research, Massachusetts Institute of Technology, accompanied by Clark A. McCartney, director of contracts and grants, University of Southern California, and Arthur A. Smith, counsel to MIT.....	305
Latker, Norman J., Patent Counsel, Department of Health, Education, and Welfare.....	15
Marcy, Dr. Willard, vice president, patent program, Research Corp., New York, N.Y., accompanied by James S. Coles, president, Research Corp.; Robert J. Sanders, Jr., counsel, invention administration program, Research Corp.; and John Garrison, treasurer, Research Corp.....	417
Miles, L.W., president, University Patents, Inc., Stamford, Conn.....	549
Morrison, Alan, counsel, Public Citizen Litigation Group, Washington, D.C.....	618

### EXHIBITS

Letter from Senator Gaylord Nelson, to Lester A. Fettig, Administrator, Office of Federal Procurement Policy, Office of Management and Budget, Mar. 17, 1978.....	4
Letter from Lester A. Fettig, Administrator, Office of Federal Procurement Policy, Office of Management and Budget, to Chairman Gaylord Nelson, Mar. 21, 1978.....	9
Letter from Norman J. Latker, Patent Counsel, Department of Health, Education, and Welfare, to Gerald D. Sturges, May 26, 1978.....	51
Federal Security Agency Order No. 110-1, section 2(b), Dec. 30, 1952.....	68
President John F. Kennedy's Memorandum on Government Patent Policy, Oct. 10, 1963, page 16.....	72
Report of the University Patent Policy Ad Hoc Subcommittee of the Executive Subcommittee of the Committee on Government Patent Policy, Federal Council for Science and Technology, July 1975.....	73



## GOVERNMENT PATENT POLICIES: INSTITUTIONAL PATENT AGREEMENTS

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MONDAY, JUNE 26, 1978

U.S. SENATE.  
SELECT COMMITTEE ON SMALL BUSINESS.  
SUBCOMMITTEE ON MONOPOLY AND  
ANTICOMPETITIVE ACTIVITIES,  
*Washington, D.C.*

The subcommittee met, pursuant to recess, at 9:30 a.m., in room 314, Russell Senate Office Building, Hon. Gaylord Nelson, chairman, presiding.

Present: Chairman Nelson.

Also present: Gerald D. Sturges, professional staff member; and Karen Young, research assistant.

Chairman NELSON. The subcommittee will please come to order.

Today the subcommittee holds the fifth and final day of its hearings on the history, legal basis, and implications of Institutional Patent Agreements—IPAs—as an implement of Government Patent Policy.

At issue is a proposed Government-wide IPA—a master agreement—to be included in Federal procurement regulations. At my request, the Administrator of the Office of Federal Procurement Policy placed a hold on the master patent agreement until July 18, so that it could be scrutinized by Congress and by the Executive Office of the President.

No agency is or will be obliged to offer an IPA to universities and nonprofit organizations covering research grants and contracts. However, an agency wishing to offer an IPA would have to use the master agreement.

If the master agreement goes into effect, the Department of Health, Education, and Welfare and the National Science Foundation would have to use it instead of the IPAs they have been using—if, indeed, they wish to continue offering an IPA.

If the master agreement does not go into effect, HEW and NSF will be free to continue using their own IPAs. Other agencies deciding to offer an IPA would presumably be free to devise their own.

In these hearings, the universities and their patent management organizations have argued that the Government-wide IPA should be allowed to go into effect, although they concede that few universities enjoy significant net income from technology transfer programs based on patent rights given to them by the Government.

One unanswered question involves ownership of—and potentially enormous profits from—DNA research inventions. The University

of California, Harvard, and other universities appear to be engaged in a scientific and commercial competition to apply DNA research techniques to the manufacture of insulin—a \$100 million market.

Today's witnesses are policymakers and policy advisers from HEW and the Executive Office of the President. They should be able to shed some light on this question and others involving the proposed Government-wide Institutional Patent Agreement.

Our first witness this morning is Dr. Donald Fredrickson, Director of the National Institutes of Health.

Dr. Fredrickson, we are very pleased to have you appear here this morning.

**STATEMENT OF DR. DONALD S. FREDRICKSON, DIRECTOR OF THE  
NATIONAL INSTITUTES OF HEALTH**

Dr. FREDRICKSON. Good morning, Mr. Chairman.

I am pleased to be with you today to discuss the National Institutes of Health's perspectives on patent policy. I will deal first with patent policy as it relates to biomedical research generally, and then discuss a specific patent policy issue—recombinant DNA inventions developed with the help of NIH funds.

Under current DHEW patent regulations, invention rights to discoveries developed under the Department's research support are normally allocated in either of two ways:

First, the Department may enter into an Institutional Patent Agreement (IPA) with a university or other nonprofit organization that has set up mechanisms for administering patents on inventions.

In 1968, the present IPAs replaced agreements developed by the Department in the 1950's. These earlier agreements proved to be non-uniform and, in some instances, inconsistent. The legal basis for the establishment of the IPA program does not rest on specific statutory authority but rather on the general authority of the Secretary to prescribe regulations and set the terms and conditions for grants and contracts.

The IPA offers the institution the first option to own all inventions made in performance of Department grants subject to a number of conditions deemed necessary to protect the public interest.

Detailed conditions are set forth for institutions to grant licenses, and a set of conditions for the distribution of royalties is included. Institutions must grant the Government a license to make the invention or have it made for governmental purposes. Under patent law, the use of patents for research purposes is not an infringement, and ordinarily the invention may be used in research without payment of royalties.

There are 72 IPAs now being administered by the Department. The Department Patent Branch reports that 167 patent applications were filed under IPAs from 1969 through the fall of 1974. Approximately \$24 million is committed by private industry to the development of inventions on the basis of licenses granted under these patents.

Second, for those institutions or organizations that have not entered into a patent agreement with the Department, a somewhat dif-

ferent procedure is followed: In this situation, determination of ownership generally is deferred until an invention has been made, at which time an institution may petition the Department for ownership of the invention or a license under the invention.

In the past, approximately 90 percent of all such petitions have been granted on the basis of a satisfactory plan proposed by the institution for developing or licensing. During the period from 1969 to the fall of 1974, the Department has reviewed 178 petitions for ownership from institutions not having IPAs and has granted 162 of them. The plans proposed by the institutions call for approximately \$53 million to be invested by private industry for development under the licenses awarded through this mechanism. Since the review of the Department's patent policies has not yet been completed, it would be premature to comment on the GSA amendment to the Federal procurement regulations mentioned in your letter of invitation to me.

Let me turn now to the subject of patenting recombinant DNA research inventions.

In June 1976, shortly before the release of the NIH guidelines on recombinant DNA research, Dr. Robert M. Rosenzweig, vice president for Public Affairs at Stanford University, sent me a letter asking NIH to review DHEW policies relating to the patenting of recombinant DNA research inventions. Dr. Rosenzweig noted that both Stanford and the University of California were applying for patent protection of recombinant DNA research inventions developed by their investigators under NIH support. However, in view of the intense public interest in this research generally, the two institutions felt the need for a formal advisory opinion by NIH on the patenting of recombinant DNA inventions developed under NIH grants or contracts. A number of other universities indicated similar interest in obtaining the official views of NIH.

Prior to making an official pronouncement of DHEW-NIH policy with respect to patenting of recombinant DNA research inventions, NIH decided to solicit comments from a broad range of individuals and institutions including the scientific community, the public, and the private sector.

The views of commentators were solicited on excluding recombinant DNA research inventions from IPAs, so that patents would be granted only for dedication to the public. Possible approaches include the following:

Recombinant DNA research inventions could be excluded from the IPAs. Alternatively, the IPA could require institutions filing patent applications for recombinant DNA research inventions to dedicate all issued patents to the public. Finally, a condition could be added to the Institutional Patent Agreement requiring institutions to assign to DHEW all recombinant DNA research inventions developed under Department support. The Department, as the patent holder, could either dedicate the patent to the public or pursue licensing, with appropriate conditions attached. There was little support among commentators for any of these options. They preferred to have DNA research inventions covered under the IPAs.



Commentator views were also solicited on the possibility of extending NIH guidelines to the private sector by requiring adherence to the guidelines through IPAs. The commentators generally supported this extension of guidelines to private industry through use of IPAs. However, a number pointed out that use of the patent system to achieve compliance with the guidelines was at best a make-shift solution, because of the difficulty in exercising regulatory control through the patent process.

A review and analysis of comments received on the question of patenting recombinant DNA inventions were completed in December 1976 and referred to the Federal Interagency Committee on Recombinant DNA Research for their attention.

The Interagency Committee, convened by the Secretary of HEW with the approval of the President, serves as a forum to review Federal policy on recombinant DNA issues. It provides coordination among the agencies on recombinant DNA activities and makes administrative and legislative proposals when appropriate.

On the committee are representatives of all Federal departments and agencies that support or conduct such research or might have regulatory authority over it.

A number of the agency representatives referred the analysis to their patent counsels. Among agencies commenting were the National Science Foundation, the Defense Department, the Department of Agriculture, the Energy Research and Development Administration, and the Department of Justice.

All agencies on the committee except Justice agreed that recombinant DNA research inventions should be handled on the same terms as other inventions under IPAs. The Department of Justice believed that, because of the great public interest in this field, ownership of any invention stemming from Government-sponsored recombinant DNA research should be held by the U.S. Government.

One question remains: Whether the subject of the patentable processes—specifically recombinant DNA techniques—is of such a distinctive nature that financial return to the inventors should be denied. This position had few advocates among the commentators. There are no compelling economic, social, or moral reasons to distinguish these inventions from others involving biological substances or processes that have been patented, even though developed partially or wholly with public funds. Such inventions include vaccines for rubella and rabies, treatments for herpes infections of the eye, and treatments for uremia. The argument that commercial development of these inventions based on patent protection assures maximum benefits to the public applies as well to the putative benefits of recombinant DNA inventions.

It is recognized that Federal patent policies are under extensive review by the executive branch and the Congress. This may lead to actions that could affect the administration of Institutional Patent Agreements generally and the conditions for recombinant DNA research inventions specifically.

It was my decision, however, that recombinant DNA research inventions developed under DHEW-NIH support should, at least for



the present, continue to be administered within current DHEW patent agreements with the universities. But such agreements should be amended to insure that, in any production or use of recombinant DNA molecules, the licensees will comply with the physical and biological containment standards set forth in the guidelines.

This decision was announced in March 1978, with the concurrence of the HEW Office of General Counsel and the Public Health Service.

Chairman NELSON. Don't they have to comply with those standards anyway?

Dr. FREDRICKSON. There is no law that requires the private sector to comply, Mr. Chairman.

Chairman NELSON. I see.

Dr. FREDRICKSON. Mr. Chairman. I would like to submit for the record the decision to which I just referred, the supporting analysis, and all of the comments received.

These documents are compiled in recombinant DNA research volume 2, documents relating to "NIH Guidelines for Research Involving Recombinant DNA Molecules," June 1976-November 1977.

Chairman NELSON. We will receive those for the record.

[The documents follow:]

June 20, 1978

RECOMBINANT DNA INVENTIONS (patent applied for)  
MADE WITH THE HELP OF HEW GRANT FUNDS

1. Dr. Curtiss, University of Alabama: Modified Microorganisms and Method of Preparing and Using Same
2. Dr. Wu et al., Cornell University: Oligonucleotides Useful as Adapters and Adapted Molecules for Cloning DNA and Method of Employing Same
3. Drs. Rutter/Goodman, University of California at San Francisco (UCSF): Recombinant Bacterial Plasmids Containing the Coding Sequences of the Insulin Gene
4. Dr. Goodman et al., UCSF: Purification of Nucleotide Sequences Suitable for Expression of Bacteria
5. Drs. Cohen/Boyer, UCSF and Stanford: A Process for Construction of Biologically Functional Molecular Chimeras
6. Dr. Gilbert, Harvard University: Induce Bacteria to Produce Rat Insulin

DHEW PATENT POLICY AS RELATED  
TO RECOMBINANT DNA

	<u>Page</u>
Letter from Donald S. Fredrickson to Dr. Robert M. Rosenzweig. . . . .	1A
The Patenting of Recombinant DNA Research Inventions Developed Under DHEW Support: An Analysis by the Director, National Institutes of Health, November 1977 . . . . .	2
Letter from Donald S. Fredrickson to Recombinant Advisory Committee, Director's Advisory Committee, and Representatives of Private Industry . . . . .	48
List of Correspondents on DHEW Patent Policy (Alphabetical) . . . . .	52
Letters on DHEW Patent Policy (Chronological) . . . . .	56

# RESEARCH NEEDS IN NEPHROLOGY AND UROLOGY

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HEARING  
BEFORE THE  
SUBCOMMITTEE ON  
HEALTH AND THE ENVIRONMENT  
OF THE  
COMMITTEE ON  
INTERSTATE AND FOREIGN COMMERCE  
HOUSE OF REPRESENTATIVES  
NINETY-FIFTH CONGRESS  
SECOND SESSION  
ON  
BIOMEDICAL RESEARCH WHICH MIGHT EVENTUALLY PROVIDE  
CURES, OR FORMS OF PREVENTION IN KIDNEY AND URINARY  
DISEASES

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JUNE 29, 1978

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## CONTENTS

Statement of—	Page
Cummings, Nancy B., M.D., Associate Director of Kidney, Urologic and Blood Diseases Program, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare .....	34
Fredrickson, Donald S., M.D., Director, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare ..	34 ✓
Gaus, Clifton R., SC. D., Director, Office of Policy, Planning and Research Health Care Financing Administration, Department of Health, Education, and Welfare .....	34, 76
Gottschalk, Carl W., M.D., Kenan professor of medicine and physiology, University of North Carolina .....	1
Lassiter, William E., M.D., professor of medicine, school of medicine, University of North Carolina .....	1, 11
Lytton, Bernard, M.D., professor of urology, school of medicine, Yale University .....	1, 21, 50
Maher, John F., M.D., professor of medicine, director, division of nephrology, University of Connecticut .....	1, 14
Whedon, G. Donald, M.D., Director, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare .....	34
Wilson, Curtis B., M.D., associate member, department of immunopathology, Scripps Clinic and Research Foundation .....	1, 18
Additional materials submitted for the record:	
Health and the Environment Subcommittee, Committee on Interstate and Foreign Commerce, publication, Research needs in nephrology and urology .....	96
Health, Education, and Welfare Department:	
Artificial Kidney-Chronic Uremia Program:	
Annual contractors' conference .....	65
Highlights of progress .....	53
History of obligations .....	52
Intramural research program—kidney related research .....	61
Peer review information .....	67
Research contracts active in FY 1977 .....	57
Cost comparison between home and clinical (incenter) dialysis .....	89
Dialysis per unit treatment cost .....	94
Distribution of training grant funds .....	45
NIH training program in the area of kidney and urinary tract disease and related research .....	44
Overseas research grants related to kidney disease and urology in FY 1977 .....	88
Secretary's authority to obtain and evaluate cost information .....	91
Lytton, Bernard, M.D., professor of medicine, school of medicine, Yale University, letter, dated July 14, 1978, to Chairman Rogers re research fellowships in urology and cost of that program .....	30
Statement by—	
Najarian, John S., M.D. ....	20
Salvatierra, Oscar, Jr., M.D. ....	215

STATEMENTS OF DONALD S. FREDRICKSON, M.D., DIRECTOR, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE, ACCOMPANIED BY G. DONALD WHEDON, M.D., DIRECTOR, NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES (NIH); NANCY B. CUMMINGS, M.D., ASSOCIATE DIRECTOR OF KIDNEY, UROLOGIC, AND BLOOD DISEASES PROGRAM, NATIONAL INSTITUTE OF ARTHRITIS, METABOLISM, AND DIGESTIVE DISEASES (NIH); AND CLIFTON R. GAUS, SC. D., DIRECTOR, OFFICE OF POLICY, PLANNING, AND RESEARCH, HEALTH CARE FINANCING ADMINISTRATION (HEW)

Dr. FREDRICKSON. Thank you, Mr. Chairman. It is a pleasure to be here today.

Mr. Chairman, I would like to emphasize several points contained within my statement and leave the balance of it to be entered into the record [see p. 37].

This comprehensive review of the state of the art in the important research areas of kidney and urinary tract diseases is an exemplary effort. It was initiated under contract in the summer of 1974 by the National Institute of Arthritis, Metabolism, and Digestive Diseases, which is the Institute with lead responsibility in the area of diseases of the kidney and urinary tract.

You have certainly heard a very competent panel with impeccable credentials and I feel they are representative of the entire committee which labored on this report and which has done a splendid job.

I would say that I find their report a conservative one. It is low key and very thoughtfully done and certainly I am in agreement with much of what the report contains.

As is your committee, I, too, am very grateful for their effort because, as you have outlined in your statements and as they have described in their testimony, the extraordinary problem represented by end-stage renal disease alone in the United States—the problem covered—is a the catastrophic one medically involving many patients, causing much pain and suffering and great cost. Clearly it is incumbent upon us that the NIH, representing the research community, evaluate our work in this area and our allocation of resources to it. Are the things that should be done being done? Should we change the manner in which we are approaching some solution to this long-standing and important problem?

The NIH, Mr. Chairman, has for more than 25 years sponsored a very broad-based research effort in diseases of the kidney. These activities have centered in several institutes. NIAMDD is the lead Institute. The Institute having the next largest investment is the National Heart, Lung, and Blood Institute, because of its interest in both vascular problems and particularly in hypertension and its ravages on the kidney. Both of these institutes and others fund fundamental studies on the physiology of the normal structure and function of the kidney and also clinical studies.

Our total expenditures for research in diseases of the kidney and urinary tract in fiscal year 1977 were approximately \$59 million, Mr. Chairman. We estimate that this is about 80 percent of the total Federal effort in regard to research in this particular area.



Mr. ROGERS. That is done through this Institute?

Dr. FREDRICKSON. All the Institutes of NIH. That is the NIH investment.

Mr. ROGERS. Fifty-nine?

Dr. FREDRICKSON. Fifty-nine million, sir, just correct somewhat over the figure of 58 which you had been provided earlier.

Now, three-quarters of the funds expended by NIH in fiscal 1977 were for investigator-initiated research. The research grant mechanism is the one, as you have just heard, the committee itself favored as the primary effort for emphasis in the approach toward this problem.

As does the committee, we also believe, after a searching analysis of our own, that investigator-initiated research is still the best approach to kidney and urinary tract diseases, since the basic causes of these disorders are still not well enough understood for effective use of more targeted mechanisms.

I think that the figure of \$59 million we have given you is a reasonable one for an attack upon a disease problem related to an enormous amount of basic research in other areas.

Undoubtedly the critical problem of immunology as it relates to immunologic kidney disease and to renal transplantation is a subject of research supported by funds that are not completely included in this figure, just as the treatment of infectious disease in a great many other areas must interdigitate with the approach to any specific organ or disease problems at NIH.

With the issuance of this report, there has been an opportunity for me to sit down with the Institutes that are involved, particularly the National Institute of Arthritis, Metabolism, and Digestive Diseases, the National Institute of Allergy and Infectious Diseases and the National Heart, Lung, and Blood Institute, to explore how well coordinated we are, what the opportunities are that lie across Institutes, the so-called trans-NIH approach which is so important in many of these problems.

We have even had opportunity to talk with the Health Care Financing Administration which you will hear from later about the many questions that relate to the causes of these diseases, how good our epidemiologic information is, where we really need to cast the net broader in order to deal more effectively with the problem. There ought to be some way to knock down the percentage of renal diseases in this country by significant increments. One question, of course, that remains is, are there causes that we really don't even suspect that are important?

We don't have good enough evidence. This is a very important problem. Yet I don't think we have exhausted it to the extent we can. Certainly the one major effort that we need to look at more critically is our coordination with other agencies in epidemiologic work.

The Institute does have epidemiologic studies which it is funding to help determine the causes of renal disease. There is an important project going on on the West Coast. There are several others we are undertaking in cooperation with the armed services and with the National Center for Health Statistics, and I think these are good first steps. We need to make sure they are strongly supported to see if we can find new clues, new insights as to where



we might look with regard to the causes of end-stage renal disease and to increase understanding of glomerulonephritis. This disease seems to be the single most important cause of renal breakdown and itself is an etiologically heterogeneous group of disorders which is simply not adequately understood.

Due to the increased treatment of hypertension today, there is a decline in mortality and morbidity from this disease—and undoubtedly we are going to see less end-stage renal disease due to this problem. It is going to be, I suspect, a beneficial fallout of achievement in that other area.

We hope we will see that same kind of trend develop in other kidney diseases resulting from other causes.

You will note the committee has spoken about immunology research as an important area for emphasis. I agree with this, as I have already indicated. There is a tremendous amount of research going on today in the area of immunology in general. It is a very hot area. I think we have to be sure we are not overlooking anything with respect to the kidney as a target organ.

I would perhaps, put emphasis on benign prostatic hypertrophy not only because it is such an important problem, but because endocrinologic research has reached an extraordinary stage of development. Certainly there must be ways we can approach that important problem with a little more ingenuity.

In addition, work is going on relating to the important area of infections of the urinary tract, and I want to make sure we don't neglect opportunities there.

The committee has discussed the issue of manpower. I can tell you in the fiscal year 1977 we were training about 155 people, man-year equivalents, in all of our programs at NIH relative to the kidney and diseases of the urinary tract.

With respect to the level of support for investigator-initiated research grants in fiscal year 1977, the, National Institute of Arthritis, Metabolism, and Digestive Diseases was able to fund about 33 percent of approved research grants in this particular area and a conservative estimate would suggest that indeed there is research of good quality, very good quality, in this area which we could not fund because we couldn't reach a higher level of support for this particular kind of investigator-initiated research.

Mr. Chairman, we do deeply appreciate the work of the participants in the study you have just heard. We welcome again the opportunity to discuss their results and opinions with you and the committee and I will be happy to answer any questions that you or Dr. Carter may have.

[Dr. Fredrickson's prepared statement follows:]

STATEMENT BY  
DONALD S. FREDRICKSON, M.D.  
DIRECTOR, NATIONAL INSTITUTES OF HEALTH

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Mr. Chairman and Members of the Committee:

Thank you for the opportunity to appear today to discuss NIH research on kidney and urinary tract diseases, and to introduce the report of the Coordinating Committee on Research Needs in Nephrology and Urology.

This comprehensive review of the state-of-the-art in these important research areas was initiated under contract in the summer of 1974 by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), the Institute at the National Institutes of Health with lead responsibility for diseases of the kidney and urinary tract. The purpose was to assess current research in these areas and to obtain guidance in developing and supporting future research efforts.

The End-Stage Renal Disease Program, federally funded through Medicare, has sharply focused Congressional and public attention on the costs of this catastrophic illness. This year the Federal Government will spend close to a billion dollars to maintain the lives of about 40,000 patients with irreversible kidney failure. The costs in terms of human suffering by these individuals and their families are even greater. In addition, many other disorders of the kidney and urinary tract are less dramatic in their outcome but temporarily or chronically disable even larger numbers of our population. Over seven million Americans suffer from chronic kidney and urinary tract disorders such as urinary tract infections and kidney stones. In any one year, we can expect over six million instances of acute kidney and urinary tract disorders, over two-thirds of which are due to some form of infection.

In view of the importance of the problems, it gives me great pleasure indeed, Mr. Chairman and Members of the Subcommittee, to be here today with some of the outstanding authorities who have been responsible for the preparation of this report. Among these are the two co-Principal Investigators, Drs. Carl W. Gottschalk and William E. Lassiter, and several other members of the coordinating committee.

The coordinating committee provided the leadership for the 11 specialty committees which were formed to undertake the study. Serving on these committees were over 100 outstanding authorities representing disciplines from fundamental as well as applied fields in kidney and urinary tract research. The committees and the reports they produced addressed the full range of kidney and urinary tract disease problems and considered the present state of knowledge, important gaps, and directions for future investigation in each aspect of the field.

As you know, Mr. Chairman, for over 25 years the NIH has sponsored a broad-based research effort in nephrology and diseases of the kidney and urinary tract. These activities are centered primarily in the NIAMDD and the National Heart, Lung, and Blood Institute (NHLBI). Our work ranges from the most fundamental studies on normal and deranged structure and function to clinical studies related to the diagnosis and management of these diseases.

In FY 1977, our total expenditure in this area was \$59 million, which we estimate to be over 80% of the Federal research effort on kidney and urinary tract diseases for that year.

Our major categories of research on these diseases fall into five areas: normal structure and function of the kidney, renal disorders, renal failure, urolithiasis (the formation of kidney stones), and urinary tract and urinary tract infections. Three-fourths of the total funds expended by NIH in FY 1977 was for investigator-initiated research. We believe investigator-initiated research is the best approach to kidney and urinary tract diseases, since the basic causes of these disorders are not well enough understood for effective use of more targeted mechanisms.

In addition, I want to assure you that there is particularly close coordination between NIAMDD and NHLBI, which together support almost 70% of kidney research at NIH. These efforts are also coordinated with the infectious and immunologic research programs of NIAID which bear on several major renal disease mechanisms and on transplant rejection. Liaison also exists between NIH and the National Center for Health Statistics.

NIH has given major emphasis to several special kidney disease areas through support of programs such as the Artificial Kidney-Chronic Uremia Program, a contract program initiated 12 years ago; the High Blood Pressure Education Program which directs public and professional attention to the need for early diagnosis and treatment of high blood pressure which is recognized as an important risk factor for kidney disease; and the newly initiated Specialized Centers of Research in Urolithiasis. In 1976, NIAMDD and the NIH Fogarty International Center



organized a special conference on "Prevention of Kidney and Urinary Tract Diseases" bringing together domestic and international experts to assess the state-of-the-art and present possibilities for improved prevention. We have also sponsored several meetings and workshops as a means to stimulate research in such understudied areas as the etiology of kidney and bladder stones. This year, the NIAID and NIAMDD are jointly sponsoring a meeting on Immune Mechanisms of Kidney Disease, an important area because of its relationship to glomerulonephritis (an inflammatory disease involving the glomeruli or filtering units of the kidney), which is the commonest cause of end-stage renal disease.

Today we know of only a few real opportunities for prevention of kidney disease and renal failure. One of these relates to kidney disease due to hypertension. During the last decade and a half, new methods of management of high blood pressure, primarily through drug therapy, have become available. Use of this therapy is expected to limit the progression of kidney disease for that proportion of patients (perhaps 15% to 20%) whose kidney failure is caused by hypertension. There is also increasing recognition in this country and abroad that overuse and abuse of analgesic drugs can lead to irreversible damage of the kidneys. Here again, preventive countermeasures against these and other drugs and environmental toxins which can damage the kidneys may reduce somewhat the extent of irreversible renal failure for some patients. Also, diagnosis and treatment of kidney infections and of the anatomical abnormalities which predispose to infection offer promise of preventing

acute kidney disease from developing into chronic and end-stage phases. In general, however, with our currently incomplete state of knowledge, we must admit that only a small part of the problem of irreversible kidney failure and end-stage renal disease can be reduced through preventive measures at the present time.

Thus, we are acutely aware of the importance of continuing efforts to understand the basic causes of kidney and urinary tract diseases. We feel dialysis and transplantation are remarkable technologic achievements to which over 40,000 Americans owe their continued lives. These treatments, however, are far from perfect. As we seek to learn more about the complex anatomic, physiologic, immunologic, and infectious causes of kidney disorders, we are also working to find ways to make transplants and dialysis more effective and to reduce cost of maintenance dialysis. In conclusion, Mr. Chairman, we are proceeding on several fronts to understand the nature and causes of these complex diseases, to develop better methods to treat them, and, we hope, ultimately to control and prevent them.

The report you have before you will be tremendously helpful in this regard. We deeply appreciate the work of the participants in this study on research needs and directions for kidney and urinary tract diseases. We wish to assure you and the many outstanding scientists and clinicians who authored this report that the NIH will make good use of the guidance the study provides.

I would be happy to answer any questions you or members of the Subcommittee may have.

Written comments and inquiries concerning the *Proposed Revised Guidelines* should be addressed to the Director, National Institutes of Health, Bethesda, Md. 20014. All comments received will be available for public inspection at the Director's office on weekdays (Federal holidays excepted) between the hours of 8:30 a.m. and 5 p.m.

Dated: July 19, 1978.

DONALD S. FREDRICKSON,  
Director,  
National Institutes of Health.

**DECISION OF THE DIRECTOR, NATIONAL INSTITUTE OF HEALTH, TO ISSUE REVISED GUIDELINES FOR RECOMBINANT DNA RESEARCH**

JULY 19, 1978.

**CONTENTS**

- Introduction and overview.
- Scope and applicability of guidelines.
- Containment.
- Containment guidelines for covered experiments.
- Roles and responsibilities.
- Organization of document and abbreviations used.
- I. Scope of the guidelines.
- Review of RAC proposed guidelines.
- Review of comments and NIH proposed guidelines.
- II. Containment.
- Physical containment.
- Review of RAC proposed guidelines.
- Review of comments and NIH proposed guidelines.
- Biological containment.
- Review of RAC proposed guidelines.
- Review of comments and NIH proposed guidelines.
- III. Containment guidelines for covered experiments.
- Review of RAC proposed guidelines.
- Review of comments and NIH proposed guidelines (general).
- Specific considerations.
- IV. Roles and responsibilities.
- Review of RAC proposed guidelines.
- Review of comments and NIH proposed guidelines.

**INTRODUCTION AND OVERVIEW**

Today, with the concurrence of the Secretary of Health, Education, and Welfare, and the Assistant Secretary for Health, I am proposing revisions to the NIH Guidelines for Recombinant DNA Research.<sup>(1)</sup> These Guidelines were first issued on June 23, 1976. The proposed revisions result from a continuing process of scientific and public exchange similar to that of the 1976 edition. This overview sketches the background for proposed revisions and summarizes the proposed changes. It references accompanying documents

and other pertinent sources of information.

The probable risks and benefits of recombinant DNA research—the larger subject of which the NIH Guidelines are a part—have been discussed in numerous forums since first addressed in 1973.<sup>(2)</sup> Congress has held multiple hearings on related issues, including proposals to convert the Guidelines to Federal regulations<sup>(3)</sup> and redefine recombinant DNA research to narrow the range of experiments subject to regulations. Early in 1977 the NIH Recombinant DNA Advisory Committee (RAC), the scientific and technical committee responsible for proposing revisions to the Guidelines, began its task of identifying changes needed in the Guidelines and forwarded suggestions to me for consideration. In order that public comments could be heard on the RAC-proposed revisions, published in September 1977,<sup>(4)</sup> a meeting of the Advisory Committee to the Director, NIH (DAC), the committee responsible for public oversight, was held in December. The extensive record of this hearing bears witness to almost unanimous agreement that the original Guidelines badly need updating, and suggests numerous directions in which revisions might move.<sup>(5)</sup>

Much of the discussion at the December 1977 meeting of the DAC affirmed the need for continuous reevaluation of the scientific premises underlying the original Guidelines. Since Asilomar,<sup>(2)</sup> growing evidence has suggested that other experts ought to review the concerns of the molecular biologists who first raised questions about the safety of recombinant DNA research. Scrutiny from experts in infectious diseases, epidemiology, virology, botany, ecology, laboratory safety, and other disciplines has been needed. NIH sponsored a workshop for this purpose at Falmouth, Mass., 6 months before the DAC meeting. Here, old and new information about *E. coli* K-12—the host most used in recombinant DNA experiments—was interpreted carefully. From this came a consensus that the chances of this host being convertible to an epidemic pathogen are negligible.

Those attending the December DAC meeting also heard complaints that containment levels were set too stringently for recombinant DNA work on viruses and plants. This applied both to the original Guidelines and to the revisions proposed in September 1977. A decision was made to address the issues through workshops without delay.

One of these workshops, held at Ascot, England, dealt specifically with viruses.<sup>(7)</sup> Here, experts from several countries, most of whom had no stake in recombinant DNA experiments,

reached an unequivocal opinion that the risks of cloning viral DNA in a bacterium like *E. coli* K-12 are not greater, and are usually much less, than the risks of handling the parent virus alone. They also stressed that defective viruses pose little risk of infection when used as vectors for cloning DNA in eukaryotic cells, since the cells cannot survive outside permissive laboratory conditions and the virus cannot escape in a viable form. A second working group, meeting in Bethesda,<sup>(7)</sup> then reviewed the conclusions. It agreed that the original Guidelines imposed stricter containment on use of viral DNA or of viruses as vectors than could be justified by any available fact, and recommended changes.

A group of agricultural scientists met in Washington, D.C., in March 1978<sup>(8)</sup> to consider the containment conditions for incorporation of DNA from plant pathogens into *E. coli* K-12 and for use of viral and other vectors in plants. An important concept discussed at this workshop is the lack of evidence that *E. coli* K-12, or any other strain of this bacterium, is capable of acquiring an ecological niche in plants and thus infecting them.

On April 27-28, 1978, the RAC considered the recommendations concerning viruses and plants and agreed with most of them. With a few changes, they are a part of the proposed revision.

At the December 1977 hearings before the DAC, other aspects of the Guidelines evoked requests for revisions.<sup>(5)</sup> There was overwhelming sentiment for exempting from the Guidelines experiments involving recombination of DNA within the same strains or from pairs of organisms that transfer genes in nature. Discretion to exempt such experiments is not provided in the original Guidelines; nor does one find there the flexibility to permit other experiments for purposes of risk assessments needed to determine the merits of particular standards, or how these should be revised. Other criticisms of the Guidelines stressed the delays and confusion created by excessive centralization of administrative control, and it is evident that implementing procedures must be changed.

Certain background elements merit comment. Shortly after the NIH Guidelines were published, the British guidelines appeared.<sup>(9)</sup> Subsequently other national guidelines have been issued, most recently those of the Soviet Union. Many international aspects of DNA research and its regulation have been reviewed elsewhere.<sup>(9)</sup> The December 1977 DAC meeting directed attention to instances where the NIH Guidelines either exclude experiments that have been conducted abroad or make them far more diffi-



cult to do.(10) Moreover, factual bases for the greater stringency of the U.S. (NIH) Guidelines cannot be shown.

Five years have passed since concerns were first raised about the hypothetical hazards of laboratory experiments with recombinant DNA. The thousands of individual applications of such techniques have produced much useful knowledge, but no evidence has come to light of a product created by these techniques that has been harmful to man or the environment. Foreign genes inserted into prokaryotic host-vector systems have been faithfully replicated and produced in quantities valuable to science. On the other hand, prokaryotes generally have not been able to translate eukaryotic genes into biologically active proteins. No new facts or unconsidered older ones have emerged to support the fears of harmful effects, and one prominent early proponent of guidelines has repudiated his support for them.(11) At the least, there is growing sentiment that the burden of proof is shifting toward those who would restrict recombinant DNA research.(12)

Although clearly the time has come to revise the original NIH Guidelines for Recombinant DNA Research, it is not the time to conclude that they are being altered in preparation for their early abandonment. Understanding of gene regulation and expression is increasing inexorably and at an awesome pace. We may predict that ways will be found to achieve and control the translation of foreign genes by a variety of hosts.(13) As the barriers to translation are dropped, some of the larger promise of recombinant technology will be realized. In some proportion to the harvest of positive results, a capability must be maintained for observing any capacity of these experiments to yield harmful products, and for communicating this to all who have an interest in similar experiments.

In preparation for this next phase of recombinant DNA research, several shifts in NIH guidance are necessary. Experiments posing no threat to safety must be exempted from the Guidelines; and provisions must be made to remove others as soon as their harmlessness becomes evident. Any universal rules imposed on this kind of activity derive validity from continual modification dictated by results of the experimentation they govern.

Primary responsibility for compliance with the rules must be located where the work is done. There it must be shared fully by principal investigators, those who work in their laboratories, institutional biosafety committees, and the institutional leaders. The NIH Office of Recombinant DNA Activities (ORDA) should be relieved of its

burden of obligatory prior approval of certain experiments, so that it can better carry out, along with the RAC, two central functions. These are the continuing synthesis and interpretation of the Guidelines, and the maintenance of full communication among all who must use them.

To recapitulate, these new proposed Guidelines arose from a proposal made to me by the RAC in September 1977. Numerous amendments have been made on the basis of public comments received at the December 1977 hearing, in extensive correspondence before and after that, and recommendations of special expert workshops whose reports were then assessed by the RAC in April 1978. The proposal and the amendments have been the products of long and intense participation by numerous persons representing many points of view. I now summarize the more important proposed changes. The basis for decision on each element of revision is provided in detail in subsequent sections of this document.

#### SCOPE AND APPLICABILITY OF THE GUIDELINES

Recombinant DNA containing synthetic sequences is now explicitly part of the definition of what is included under the Guidelines. The standards of the Guidelines now apply to all recombinant DNA experiments conducted in an institution that receives any support from NIH for recombinant DNA research. This includes a registration requirement.

The original Guidelines contain a number of prohibited experiments. There was little sentiment for the removal of all the original prohibitions—although it has been noted that the U.S. (NIH) Guidelines are the only national guidelines to stipulate "prohibited" activities. The original prohibitions, with one modification and a necessary "flexibility" clause,(14) are therefore retained in the proposed revision. They immediately precede a new section called "Exemptions"—a juxtaposition chosen to emphasize that the prohibitions still override.

The first exemption from the guidelines covers the handling of DNA outside a host organism or virus. Such "naked DNA" has been handled in laboratories for years and is rapidly inactivated in nature.

The exempted experiments of the second class consist essentially in rearranging, or deleting from, molecules of nonchromosomal or viral DNA. No foreign DNA is involved. An example would be the introduction of a DNA molecule formed from pieces of SV40 virus into eukaryotic cells in tissue culture. Since there is little if any basis for presuming such "rearrangement"

or "deletion" experiments to be hazardous, they are now excluded.

A third class of exemptions are experiments called "self-cloning," in which DNA found naturally in a host may be reinserted into that host. These are reproductions in the laboratory of events that occur in nature.

Similarly, provision is made in the proposed guidelines for exemption of a fourth class of experiments that involve donor-host pairs that normally exchange DNA. Such genetic exchange is known to occur widely between various species of bacteria and is generally mediated by certain plasmids or viruses. Experimental recombinations of this type are only an imitation of what nature is able to accomplish handily in the absence of Federal regulation. A list of donor-host pairs to be exempted is begun in this revision and will be expanded periodically as knowledge grows. The initial choice from several possible lists submitted to me by the RAC is a conservative one, restricted to pairs of organisms for which there is documented evidence of natural exchange.

Finally, a fifth exemption is provided for removal of other recombinations when they are shown to be safe. The last two exemptions create some of the discretionary power for modifying the guidelines that was so lacking in the original. Provision will be made for public input to such decisions, either by announcement of proposed exemptions prior to consideration by the RAC or before a decision by the Director becomes effective.

#### CONTAINMENT

I have made one decision that will not be regarded with equal pleasure by all engaged in recombinant DNA research. P1 containment previously permitted mouth pipetting. In accord with a previous recommendation by the European Molecular Biology Organization (EMBO), its virus Working Group strongly recommended prohibiting this practice; and so did NIH safety advisors. The RAC at its meeting on April 27-28, 1978, recommended that mouth pipetting be prohibited only for those P1 recombinant DNA experiments involving viral DNA. Rather than create two separate classes of P1, and in recognition of the present availability of excellent mechanical devices for pipetting, I am proposing that mouth pipetting no longer be permitted in P1 containment. Since it is already prohibited in P2-P4 containment, this bans the use of mouth pipetting for any experiment covered by the Guidelines.

#### CONTAINMENT GUIDELINES FOR COVERED EXPERIMENTS

The recommendations of the RAC, arising from the Ascot-Bethesda work-



shops, represent the first realistic appraisal of any hazards that might lie in the use of viral vectors or the cloning of viral DNA. Recombinant techniques offer access to areas of viral biology that are vitally important. Such studies should not be impeded unnecessarily. I have accepted the April 1978 recommendations of the RAC in this area with minor amendments. The revised guidelines emphasize the current dictum that any hazards of working with viruses in recombinant DNA experiments are maximal at the first stage, when the virus itself with its full genomic complement is handled.

The RAC unanimously approved modest changes in containment for plant experiments. I have also approved them provisionally, contingent upon concurrence by the Department of Agriculture.

A new sentence has been added to the guidelines giving much needed flexibility in the setting of containment levels.(15)

#### ROLES AND RESPONSIBILITIES

Two years' experience with the guidelines has offered valuable tutelage in the limits of external (Federal) control of laboratory experimentation. Scientists and their co-workers have long experimented with pathogenic organisms, poisonous plants and animals, and hazardous chemicals. The laboratory is not among the more notorious occupational settings for accidents or illness, and damage to community or environment by basic laboratory research is almost unknown. Control over the use of radioisotopes in the laboratory, long a Federal preserve, is not comparable to use of recombinant DNA techniques; for the risks of using radioisotopes are calculable and mistakes are easily measured. Thus realistic and durable standards can be set. Without a base for the setting of such standards, conventional regulation is difficult at best, and at worst can be preposterous.

In the case of recombinant DNA technology, we are in the midst of a search for any risks, and thus for applicable standards. The scientists who raised the possibility of risks also realized that the only effective safeguards lay in a maximum enhancement of the collective nature of the scientific process. The usual communications networks of science had to be augmented and the evaluation of results and the reaching of consensus accelerated. These actions, as was reasoned, would help establish a set of initial rules, and there was the added assumption that they could and should be kept up to date. All using the new techniques would sign a "memorandum of understanding" to the effect that, until things became clearer, the basic com-

munity of scientific inquiry would be especially emphasized in any work with recombinant DNA techniques.

The power of the Government to require such discipline of its grantees was an attractive reason for the scientists to request Federal intervention. And the Federal capacity to achieve the essential communication and consensus-building has been one of the most positive results of this experiment in administration. But the price of Federal intervention includes a heavy tax of formalism. In the instance of these guidelines, diverse pressures have made difficult the appropriate balancing of substance and procedure. I have already alluded to one of the undesirable results—a chilling inflexibility of the original guidelines—and its proposed correction by revision.

Prior NIH clearance is mandatory for new NIH grants and contracts involving recombinant DNA techniques and for all projects in P4 facilities. In the proposed revised guidelines, prior NIH clearance is no longer required for changes at the P1-P3 levels. These changes must be approved by the institutional biosafety committee (IBC), and NIH will then review the IBC actions. This proposal reverses an October 1977 issuance stating that changes in ongoing projects require prior NIH clearance. The requirement resulted in numerous delays in projects which could not be justified on grounds of safety.

The proposed guidelines would strengthen institutional responsibilities and authorities in determining compliance. A full partnership with all investigators and their institutions is intended. The role of the IBC is particularly enhanced through delegation of some discretionary powers that were previously reserved for NIH and the RAC. To better meet these obligations, an institution using P3 or P4 containment is required under the proposed guidelines to have a qualified biological safety officer.

Experience gained in the past 5 years in explaining recombinant DNA technology has shown how valuable can be a community's activities. At least one member of the IBC is to be a "public member"—i.e., one who has no financial connection with the institution. Further, to ensure opportunity for public participation at the national level, procedural are set forth, as explained in Part IV of the decision, that provide public notice and solicit comment on the major actions of NIAH.

Another stipulation of the revised guidelines is that failure of compliance can lead to suspension of NIH support for recombinant DNA research.(16)

Provision is now made for the private sector to register voluntarily its recombinant DNA activities with NIH.

Also, other consulting services, including certification of host-vector systems, will be provided. The service will be accompanied by protection of proprietary data as mandated by law.

NIH issued a draft environmental impact statement on the guidelines in September 1976. This was revised after public comment and issued in final form in October 1977. It concluded that the activities covered by the guidelines had no predictable impact on the environment, since all the risks discussed were hypothetical. The EIS was examined by a Federal district court in 1978.(17)

In parallel with the process of revising the guidelines, NIH has conducted an environmental impact assessment, including an analysis of how current experiments supported by NIH will be affected by this revision. Again, the activities covered by the revised guidelines deal only with hypothetical risks, and thus the assessment reveals no predictable impact on the environment. Its content is published herewith in a companion document.

#### ORGANIZATION OF THE REMAINDER OF THIS DOCUMENT AND ABBREVIATIONS USED

The Recombinant DNA Molecule Program Advisory Committee is sometimes referred to below as the Recombinant DNA Advisory Committee or Recombinant Advisory Committee or RAC.

The meeting of the Advisory Committee to the Director, NIH, which took place in December 1977 is sometimes referred to below as the meeting of the Director's Advisory Committee or of the DAC or the December 1977 public hearing.

The "NIH Guidelines for Research Involving Recombinant DNA Molecules" as issued on June 23, 1976, and publishes in the *FEDERAL REGISTER* on July 7, 1976, are sometimes referred to below as the original guidelines or the 1976 guidelines or the current guidelines.

The proposed revised guidelines prepared by the RAC and published in the *FEDERAL REGISTER* on September 27, 1977, are referred to below as the PRG-RAC.

The proposed revised guidelines which are being proposed now by NIH are referred to below as the PRG-NIH.

The remainder of this document is divided into four parts corresponding to the four parts of the guidelines; i.e., I. Scope of the Guidelines; II. Containment; III. Containment Guidelines for Covered Experiments; and IV. Roles and Responsibilities.

Within each of these four parts there are two subsections; i.e., Review of RAC-Proposed Guidelines and Review of Comments and NIH-Proposed Guidelines. The first subsection



describes how the PRG-RAC differs from the 1976 guidelines; the second describes (1) the public comments received both before and after the December 1977 DAC meeting, concerning the PRG-RAC, and (2) the changes which have been made in response to these comments leading to the PRG-NIH.

#### FOOTNOTES TO INTRODUCTION AND OVERVIEW

(1) In addition to the proposed revised guidelines and this "Decision Document," there is also being released an Environmental Impact Assessment, including numerous appendices.

(2) The capability to perform DNA recombinations, and the potential hazards, had become apparent to scientists at the Gordon Research Conference on Nucleic Acids in July 1973. At their behest the National Academy of Sciences created a committee that organized an international conference held in February 1975 at Asilomar Conference Center, Pacific Grove, Calif. Approximately 150 scientists, of whom a third were from foreign countries, were present. The committee also called on the National Institutes of Health to establish an advisory committee to draft guidelines for the conduct of this research. Temporary guidelines were issued at Asilomar pending issuance of NIH guidelines.

In response, the NIH Recombinant Advisory Committee (formally "NIH Recombinant DNA Molecule Program Advisory Committee") was established in October 1974 to advise the Secretary of HEW, the Assistant Secretary for Health, and the Director of NIH to accomplish these tasks. The several meetings at which the Recombinant Advisory Committee developed its proposed guidelines in 1975 were announced in the *FEDERAL REGISTER* and were open to the public. The committee, after preparing several draft versions of guidelines, reached agreement

on a recommended revised version, which was referred to the NIH Director for review in December 1975.

A special meeting of the public advisory Committee to the Director, NIH, was convened in February 1976 to review these proposed guidelines. In addition to current members of the committee, a number of former committee members as well as other scientific and public representatives had been invited to participate. There was ample opportunity for comment and an airing of the issues, both by the committee members and the public witnesses. All major points of view were broadly represented.

The proposed guidelines were reviewed by the Director, NIH, in the light of comments and suggestions made at the public hearing as well as extensive written correspondence received after the meeting. When the final guidelines were released in June 1976, an accompanying decision paper described in great detail all relevant public comments and the reason for accepting or rejecting specific recommendations in preparing the final guidelines. The NIH guidelines and the Decision of the Director, NIH, were published in the *FEDERAL REGISTER* on July 7, 1976. In addition, copies of the guidelines were widely distributed to foreign embassies, medical and scientific journals, NIH grantees and contractors, and professional research societies.

(3) The following committees have held hearings and/or markup sessions on Recombinant DNA legislation:

House—The Subcommittee on Health and the Environment and its parent, the Committee on Interstate and Foreign Commerce; the Subcommittee on Science, Research, and Technology and its parent, the Committee on Science and Technology.

Senate—The Subcommittee on Health and Scientific Research and its parent, the Committee on Human Resources; the Subcommittee on Science, Technology, and Space. Its parent, the Committee on Commerce, Science, and Transportation, has not held any hearings or markup sessions on this topic.

The following bills on recombinant DNA technology have been formally introduced:

(4) The Recombinant Advisory Committee considered its proposed revisions at meetings throughout 1977. The version proposed to the Director, NIH, in September 1977, appeared in the *FEDERAL REGISTER* on September 27, 1977.

(5) This meeting of the Director's Advisory Committee took place in Bethesda on December 15-16, 1977. A summary of the meeting appeared in the recombinant DNA technical bulletin, and the complete record will shortly be published by NIH in vol. 3 of the series recombinant DNA research.

(6) The NIH-sponsored meeting at Falmouth, Mass., on June 20-22, 1977, was chaired by Dr. Sherwood Gorbach. A complete record of this meeting appears in the "Journal of Infectious Diseases" (May 1978).

(7) The "U.S.-EMBO Workshop to Assess Risks for Recombinant DNA Experiments Involving the Genomes of Animal, Plant, and Insect Viruses" was held on January 26-28, 1978, in Ascot, England. It was attended by experts on viruses from the United States, Britain, and other European countries, a majority of whom were not engaged in recombinant DNA research. The primary purpose of the meeting was to conduct a scientific and technical analysis of possible risks associated with cloning eukaryotic viral DNA segments in *E. coli* K-12 host-vector systems and with the use of eukaryotic viruses as cloning vectors in animal, plant, and insect systems. The report of the workshop was published in the *FEDERAL REGISTER* on March 31, 1978, and appears as appendix E to the accompanying environmental impact assessment. The results of the Ascot meeting were then reviewed by another group of U.S. virologists who converted them into recommendations for revision of the guidelines. This working group was chaired by Dr. Harold Ginsberg and met on April 6-7, 1978. Its report appears as appendix F to the accompanying environmental impact assessment. The report was considered by the Recombinant Advisory Committee at its April 27-28, 1978, meeting.

(8) The "Workshop on Risk Assessment of Agricultural Pathogens" was held on March 20-21, 1978, in Washington, D.C., under the auspices of the National Science Foundation, the Department of Agriculture, and the National Institutes of Health. A copy of the report of this workshop appears as appendix G to the accompanying environmental impact assessment.

(9) The United Kingdom guidelines, also known as the "Williams report," were issued in August 1976. A fairly comprehensive review of the international aspects of recombinant DNA research, including issuance of national guidelines, is contained in the "Report of the Federal Interagency Committee on Recombinant DNA Research: International Activities," November 1977. This is available from the Office of Recombinant DNA Activities, National Institutes of Health, Bethesda, Md. 20014.

(10) Under the NIH guidelines, experiments using prokaryotic hosts other than *E. coli* K-12 are severely limited whereas such experiments are proceeding in Europe, especially with *Bacillus subtilis*. Certain other categories of experiments require, according to the NIH guidelines, either P4-EK2 or P3-EK3 containment. Since no EK3 system

Bill	Chief sponsor	Date
<b>House:</b>		
H. Res. 131.....	Richard Ottinger, Democrat of New York.	Jan. 19, 1977.
H.R. 3191.....	Identical to S. 621.....	Feb. 7, 1977.
H.R. 3591.....	do.....	Feb. 16, 1977.
H.R. 3592.....	do.....	Do.
H.R. 4232.....	Stephen Solarz, Democrat of New York.	Mar. 1, 1977.
H.R. 4759.....	Paul Rogers, Democrat of Florida..	Mar. 9, 1977.
H.R. 4849.....	do.....	Mar. 10, 1977.
H.R. 5020.....	Identical to S. 621.....	Mar. 14, 1977.
H.R. 6158.....	Administration bill.....	Apr. 6, 1977.
H.R. 7418.....	do.....	May 24, 1977.
H.R. 7897.....	do.....	June 20, 1977.
H.R. 11192.....	Rogers and Harley Staggers, Democrats of West Virginia.	Feb. 28, 1978.
<b>Senate:</b>		
S. 621.....	Dale Bumpers, Democrat of Arkansas.	Feb. 4, 1977.
S. 945.....	Howard Metzenbaum, Democrat of Ohio.	Mar. 8, 1977.
S. 1217.....	Administration bill.....	Apr. 1, 1977.
S. 1217.....	As reported; accompanied by Report 95-359.	July 22, 1977.
S. 1217.....	Amendment 754 in the nature of a substitute.	Aug. 2, 1977.
S. 1217.....	Amendment 1713 in the nature of a substitute.	Mar. 1, 1978.



has as yet been certified and since the first P4 facility has only recently been certified, these experiments were effectively forbidden. The same experiments require significantly lower containment under some European guidelines.

(11) Prof. James Watson, in testimony at the December 1977 DAC meeting and in print, has sought repentance for his earlier activities in support of special precautions for recombinant DNA research.

(12) The report, "Science Policy Implications of DNA Recombinant Molecule Research," March 1978, of the Subcommittee on Science, Research, and Technology of the Committee on Science and Technology, U.S. House of Representatives, says, "The burden of proof of safety factors should not be borne exclusively by proponents of recombinant DNA research; opponents must assume a corresponding burden."

(13) Significant differences exist between prokaryotes and eukaryotes in the ways proteins are synthesized under genic direction, and these account for limitations on the apparent success of many recombinant DNA experiments to date. A major thrust of current recombinant DNA research is in the direction of overcoming these differences. There is every reason to believe that this research will succeed. At my invitation, Dr. Malcolm Martin of NIH has drawn up this brief analysis of the state-of-the-art:

The potential use of recombinant DNA techniques to produce biologically useful reagents is predicated on: (a) the faithful replication of a segment of foreign DNA in a new host cell; (b) the synthesis of messenger RNA (mRNA) complementary to the inserted DNA; and (c) the efficient translation of the mRNA into a polypeptide. In nearly all cases that have been examined to date, DNA, from both eukaryotic and prokaryotic sources, has been amplified in prokaryotic host-vector systems. The fidelity of this entire process (a, b, and c) has been verified in several instances in which prokaryotic DNA segments have been cloned in *E. coli* and resulted in the synthesis of new polypeptides. Thus, in such cases, the informational content contained in the inserted prokaryotic DNA is expressed as evidenced by the synthesis of mRNA and novel proteins.

With few exceptions (some yeast inserts) the expression of eukaryotic DNA in the form of biologically active or biochemically detectable polypeptides in prokaryotes has not been demonstrated using chromosomal DNA inserts and unmodified vectors. In nearly all cases where the system has been rigorously examined, it has been shown that eukaryotic DNA has replicated in *E. coli*; in some instances, RNA complementary to the inserted eukaryotic DNA has been identified.

**Messenger RNA synthesis and function in *E. coli*.** The synthesis of messenger RNA (mRNA) in a prokaryote, such as *E. coli*, proceeds in a linear fashion along the DNA template of individual gene segments or groups of related genes. In nearly all cases examined, the mRNA molecules are the faithful colinear transcripts of prokaryotic genetic information and can be used in an unmodified form to direct the synthesis of prokaryotic polypeptides. The informational content of mRNA corresponds directly to

the nucleotide sequence of DNA in such systems (i.e., all nucleotides present in a prokaryotic gene are transcribed into messenger RNA which, in turn, programs the synthesis of a corresponding protein). Control of this phase of gene expression appears to be solely at the level of RNA synthesis.

In prokaryotes (and eukaryotes), nucleotide sequences preceding the sequences corresponding to the actual genes play a major role in determining (a) whether a given DNA sequence will be transcribed into RNA and (b) whether the RNA so synthesized will efficiently bind to ribosomes, a prerequisite for protein synthesis. For example, certain DNA sequences interact with regions of RNA polymerase and thereby participate in the initiation of RNA synthesis; they are not represented in the final RNA product. DNA sequences specifying binding to ribosomes are physically located between those for initiation of RNA synthesis and sequences encoding the amino acids of a particular protein (the gene) and are also contained in the functional mRNA molecules.

**Messenger RNA synthesis and metabolism in eukaryotes.** Our understanding of gene regulation and expression in eukaryotic cells has increased markedly during the past 10 months. A common feature of all systems that have been carefully evaluated is that the initial, faithful RNA copy of the DNA is extensively modified to produce a functional form of mRNA. The final mRNA contains only a fraction of the sequences present in the original RNA product. That is to say, portions of large RNA molecules are removed by mechanisms that are, at present, poorly understood and the remaining segments of the primary RNA transcript are then rejoined to one another. In nearly all cases an RNA segment containing a ribosomal binding site is joined to a segment coding for a polypeptide, in addition, larger gene segments are often joined together. This process was first observed in animal virus systems (1, 2) where it was shown that viral mRNA, containing the information for a product which had been previously mapped to a specific locus on the viral genome, was complementary to regions of the viral DNA which were separated by more than a thousand nucleotides.

Support for the concept of complex modification leading to functional mRNA in eukaryotic cells has recently come from recombinant DNA experiments in which chromosomal DNA has been cloned in *E. coli*. When individual cloned eukaryotic genes are carefully analyzed, intervening DNA sequences which interrupt the actual sequence of the gene in chromosomal DNA have been identified. To date, such intragenic DNA has been detected in ovalbumin (3, 4),  $\beta$  globin (5, 6), immunoglobulin (7), and even tRNA genes (8). In one instance it has been clearly shown that the intervening DNA sequences, present in the primary RNA transcript of  $\beta$  globin DNA, are absent in  $\beta$  globin mRNA (5). These mechanisms presumably function in some regulatory fashion to modulate eukaryotic gene activity.

#### IMPLICATIONS FOR RECOMBINANT DNA RESEARCH

A. The discovery of the existence of complex processes involved in the maturation of

mRNA eukaryotic cells and the demonstration of intragenic DNA in several eukaryotic genes suggests that: (1) cloning of chromosomal DNA in *E. coli* DNA (shotgun or purified) will pose little, if any, risk since the maturation mechanisms have never been observed in prokaryotes; and (2) investigators who wish to develop prokaryotic cloning systems for the purpose of synthesizing useful biological products will utilize cDNA copies of functional mRNAs or synthetic DNA with a nucleotide sequence derived from a known amino acid sequence as DNA inserts.

B. Vectors are currently being "engineered" to ensure efficient transcription and translation of DNA inserts. Using slightly different approaches, groups in San Francisco and at Harvard (9-11) are preparing DNA segments which: (1) contain the sequences necessary for interaction with *E. coli* RNA polymerase linked closely to (2) sequences which encode a bacterial ribosome binding site. Such DNA segments can then be added to a prokaryotic cloning vector next to the site into which a foreign DNA will be inserted. This arrangement will facilitate the transcription of the inserted DNA and enable the mRNA so synthesized to bind to bacterial ribosomes. This embellishment has already been used to maximize the expression of a bacteriophage gene and human somatostatin DNA in a plasmid vector system (10, 11).

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(14) Prohibition (i) in the original guidelines forbids experiments with "oncogenic viruses classified by NCI as moderate risk." The absence of evidence that use of these viruses will lead to formation of agents harmful to man and the potential for obtaining useful new knowledge, relevant to carcinogenesis in particular, and genetics in general, supports the removal of the prohi-



bition. The removal of this prohibition was proposed in the report of the Working Group on Viruses which met on Apr. 6-8, 1978, and endorsed by the RAC at its Apr. 27-28, 1978, meeting. The reasoning behind this is that recombinant DNA experiments with pieces of these viruses cloned in *E. coli* K-12 pose no more risk, and actually appear to pose clearly less risk, than work with the whole infectious virus itself. Since NCI recommends that work with these whole viruses not be prohibited, but rather be performed under containment conditions similar to P3, there is no scientific reason to prohibit recombinant DNA work with these viruses. The "flexibility" clause refers to power of the Director, NIH, to waive prohibitions when the public interest may be served by such action.

(15) The Guidelines say at the beginning of Pt. III, "Given below are containment guidelines for permissible experiments. Changes in these levels for specific experiments (or the assignment of levels to experiments not explicitly considered in this section) may be expressly approved by the Director, NIH, on the recommendation of the Recombinant DNA Advisory Committee." Insertion of such language into the guidelines was recommended by the RAC at its Apr. 27-28, 1978, meeting. It recognizes that the classification of experiments given in Pt. III will necessarily be imperfect, as investigators in the future devise new ways to conduct recombinant DNA experiments not currently foreseen and therefore not explicitly considered in the guidelines. Also, new data may become available showing that certain particular experiments currently assigned a particular containment level are, indeed, clearly more (or less) safe than envisioned at this time.

(16) See App. C to the guidelines and Part IV of this "Decision Document."

(17) In May 1977, a resident of Frederick, Md., brought suit in the U.S. District Court for the District of Columbia to enjoin a proposed risk-assessment experiment which was about to be undertaken in a maximum containment facility (P4) located at the Frederick Cancer Research Center. (*Mack v. Califano*, Civil Action No. 77-0916). On February 23, 1978, the court issued a decision refusing to grant the injunction. In so doing, the court observed that the environmental impact statement on the original guidelines constituted a "hard look" at recombinant DNA research performed in accordance with the guidelines. The court further noted that compliance with the guidelines, it appeared, would insure that no recombinant DNA molecules would escape from the carefully controlled laboratory to the environment, and that the guidelines "represent an effort by many scientists to evaluate the hazards and provide safe methods for their control."

The plaintiff appealed (Appeal No. 78-1156), and on Mar. 8, 1978, the Court of Appeals for the District of Columbia upheld the district court decision.

## I. SCOPE OF THE GUIDELINES

### REVIEW OF RAC-PROPOSED GUIDELINES

It was the determination of the Recombinant Advisory Committee that advances in knowledge pertaining to recombinant DNA activities in past years warranted significant revisions in the "purpose," "definition," and

"prohibition" sections of the NIH guidelines. A comparison of the "purpose" language of the two sets of guidelines<sup>1</sup> reveals that the standards in the PRG-RAC were meant to pertain to recombinant DNA molecules in organisms. The analogous language in the 1976 guidelines addresses recombinant DNA molecules whether or not they are contained within a cell or virus. The rationale for this change is that DNA by itself (commonly referred to as "naked" DNA) is extremely unlikely to be hazardous under experimental conditions, as it is rapidly inactivated in nature.

The definition in the PRG-RAC consisted of two parts: (1) an operational definition of recombinant DNA and (2) a qualification that the guidelines would pertain only to "novel" recombinant DNA's. The operational definition does not differ significantly from that in the original guidelines.

The second part, however, called for the creation of a list of organisms that exchange genetic information in nature, commonly referred to as "non-novel exchangers." Recombinant DNA formed with DNA from such organisms would be exempted from the provisions of the PRG-RAC, with the rationale that there is no justification for requiring containment procedures for the handling of recombinations that occur regularly in nature and are not known to be associated with any special hazards.

The provision of an open-ended listing was recommended rather than issuance of a blanket exemption, because this would allow the RAC and NIH to consider evidence that (1) the putative gene transfers do take place naturally and (2) their exemption from the guidelines is justifiable (see footnote 1 of the PRG-RAC).

Although the PRG-RAC deals with prohibited experiments under Part III, this decision document, for purposes that become apparent below, will consider the definition, exemptions, and prohibitions together under section I.

The "prohibitions" section was called section III-A, "Experiments That Are Not To Be Performed," in both the 1976 guidelines and PRG-RAC. Changes from the 1976 guidelines, proposed in the PRG-RAC, included minor wording changes in items (iii), (iv), and (vi).

The ability to grant exemptions for certain experiments from the "prohibitions" was limited in the 1976 guidelines to only the sixth prohibition (large-scale experiments with recombinant DNA's known to make harmful products). In the PRG-RAC the Direc-

tor, NIH, is given the authority to grant exceptions from any of the six prohibitions. Such a determination must be based upon the recommendation of the RAC, and weight must be given in the decisionmaking "both to scientific and societal benefits and to potential risks." The rationale for this proposed change was the desire of the RAC not to preclude the possibility of conducting such experiments for some compelling social or scientific reasons—for example, risk-assessment experiments.

The sections of the PRG-RAC dealing with purpose of the guidelines, definition of recombinant DNA, exemptions, and prohibitions evoked a great deal of comment both before and after the December 1977 public hearing. An analysis of these comments and my decision in response to the issues raised are presented in the following section.

### REVIEW OF COMMENTS AND NIH-PROPOSED GUIDELINES

There was considerable discussion at the public hearing over the scope of the guidelines. Some felt that the guidelines were too narrow in their preoccupation with recombinant DNA, as there exist other forms of genetic research capable of producing organisms of unknown potential hazard. It was further suggested that the title of the guidelines be modified to reflect the preoccupation with experiments involving prokaryotes and cells in culture, and that a companion document be released dealing with higher eukaryotes. On the other hand, it was also argued that genetic research has now received attention far beyond its due, and that other matters of experimentation await their turn.

While it is true that other techniques in genetic research, such as cell fusion and chromosome transfer, may result in formation of recombinant molecules, I do not believe at this time that we should mandate or extend the guidelines to these research areas. There are inherent in these techniques a range of natural barriers to the formation of hazardous organisms which apparently afford adequate containment, making unnecessary the issuance of Federal standards. I base this conclusion on the fact that such techniques have been used in the laboratory for decades with no known harmful effects on either the public health or the environment. I should also emphasize that the entire area of laboratory safety is of primary concern to NIH and is the subject of constant review and attention. A description of NIH activities in these areas is presented in the environmental impact assessment.

A commentator suggested that the language be deleted stating that "• • •

<sup>1</sup>The current guidelines as published in the FEDERAL REGISTER, July 7, 1976 (41 FR 27902), and the RAC's proposed revisions (PRG-RAC) as published in the FEDERAL REGISTER, Sept. 27, 1977 (42 FR 49596).



the revised guidelines [have] the intent of erring on the side of caution." While believing that the guidelines are, and should be, deliberately restrictive, I agree with the criticism that scientists should not enter into an activity with the intent of erring. The PRG-NIH now reflects this opinion by deletion of this phrase.

Another commentator suggested that the guidelines should contain language requiring all publications dealing with recombinant DNA activities to include a description of the physical and biological containment procedures used. While the PRG-NIH urges "that all publications dealing with recombinant DNA work include a description of the physical and biological containment procedures employed," NIH is not well advised to dictate to researchers or editors what must be included in a scientific publication.

There were several suggestions that the purpose of the guidelines be more clearly stated and that terms be more precisely defined. I have, therefore, added considerable new material to Part I of the PRG-NIH, renamed "Scope of the Guidelines," and divided it into the following sections, each of which is discussed further below: Purpose; Definition of Recombinant DNA Molecules; General Applicability; Prohibitions; Exemptions; and General Definitions.

#### *Purpose*

The introduction to the 1976 guidelines states that "the purpose of these guidelines is to recommend safeguards for research on recombinant DNA molecules." As noted above, to eliminate "naked" recombinant DNA from the guidelines, the PRG-RAC proposed this passage to read that the purpose is to "establish procedures for handling organisms and viruses containing recombinant DNA molecules."

This proposed revision would have had the effect of removing from coverage by the guidelines certain experiments which are prohibited by the 1976 guidelines—for example, deliberate formation of naked recombinant DNA containing genes for the biosynthesis of potent toxins. I have decided to resolve this issue conservatively. The language in the PRG-NIH, therefore, clearly states that the guidelines are intended to pertain to the construction and handling of naked recombinant DNA molecules as well as of organisms and viruses containing such molecules.

#### *General applicability*

Many commentators urged that a statement of general applicability of the guidelines be included in an early part. The issues relate to (1) the applicability of the guidelines to non-NIH funded research with recombinant DNA at institutions receiving NIH

funds for this purpose, (2) the applicability of the guidelines to NIH-supported recombinant DNA research conducted in foreign countries, and (3) the location of responsibility for insuring compliance with the guidelines. Therefore, a section entitled "General Applicability" now appears after the "Purpose" section in Part I of the PRG-NIH.

The existence of guidelines for recombinant DNA research assumes their general application. Partial adherence within an institution would defeat the purpose of extending maximal protection to the community. Thus, it would be inconsistent for NIH to provide funds for biomedical research activities to an institution that did not meet the standards of the guidelines in all of its recombinant DNA research, regardless of the source of funding. This principle is now stated explicitly in the PRG-NIH, and we intend to consider withholding NIH funds as a sanction against violation.

Rules must be established for the conduct of recombinant DNA activities funded by NIH in other countries. Generally, the requirements in force in those countries shall apply. A memorandum of understanding and agreement (MUA) must still be filed with NIH, indicating specifically which guidelines will govern the activities; and NIH reserves the right to withhold funding if the safety practices to be employed are not comparable to the NIH guidelines. An explicit statement about this has been inserted in the PRG-NIH.

Part IV of the PRG-NIH describes the responsibilities of all individuals and organizational entities involved in the conduct and review of a recombinant DNA activity. Two years of experience with administering the NIH guidelines has indicated that the ultimate responsibility for insuring compliance must be borne by the institution where the research is being done. This implies some discretion under well-defined limits for interpretation of common standards, and imposes a requirement for local expertise other than the investigator's. Accordingly, Part I of the PRG-NIH now requires that an individual receiving NIH support for recombinant DNA research be associated with an institution that is willing and able to accept the responsibilities and conditions of local governance, described more fully in Part IV of the PRG-NIH.

#### *Definition of recombinant DNA molecules*

It became apparent from the comments received that the PRG-RAC definition was inadequate in that it did not address the handling of recombinant DNA molecules containing seg-

ments of chemically synthesized DNA. I have decided that the most effective way to achieve this objective is simply to include "natural or synthetic DNA" in the definition of a recombinant DNA molecule, and this has been inserted in the PRG-NIH definition. A new section, therefore, has also been added to Part III of the PRG-NIH giving containment levels for work with recombinant DNA molecules containing synthetic DNA.

I have also revised what I perceived to be an ambiguity in the PRG-RAC definition by including within the PRG-NIH definition language explicitly stating that DNA molecules which result from the replication of recombinant DNA molecules are subject to the safety provisions of the guidelines.

Finally, no other provision of the PRG-RAC definition evoked as much comment as did the wording to exclude "non-novel" recombinant DNA from the standards. The ambiguity of such phrases as "known to exchange chromosomal DNA" and "by natural physiological processes" was strongly noted, and I agree with the commentators that we must strive for a greater degree of clarity and objectivity. Thus, it has been decided to eliminate in the PRG-NIH the two conditions cited above as criteria for exemption from the guidelines. Staff discussions of the public comments made it clear that inclusion of exemption provisions within the definition itself was not desirable. Several attempts at appropriate language did not bear careful scrutiny.

Given this situation, and also my opinion that certain categories of recombinant DNA experiments are indeed so apparently free of causing harm that they should not come under the guidelines, it was my decision to remove the criterion of "novelty" from the definition and use it as a basis for the development of a new section entitled "Exemptions."

#### *Exemptions*

The nature of the public comments on the PRG-RAC exclusion of non-novel exchangers can be divided into categories—those that pertain to the proposed standards and those to the proposed process.

The standards proposed by the PRG-RAC were that novel recombinant DNA's are those consisting of "segments of any DNA from different species not known to exchange chromosomal DNA by natural physiological processes . . . In general recombinant DNA molecules . . . will not be considered novel when all the components are derived from genomes known to replicate within the organism used to propagate the recombinant DNA." This is qualified, however, by a footnote stating that the "recombinant DNA formed between segments of eu-



karyotic viral DNA and any eukaryotic DNA . . . shall not be excluded . . . until such time as there is more information about the extent of naturally occurring recombinational events between these DNAs."

The public comments on these standards raised the following issues:

- That safety rather than novelty should be the criterion for exclusion; that is, any recombinant DNA molecule that poses a threat to the public health or the environment should be covered by the guidelines regardless of whether the molecule is a novel one.

- Others argued that the proper criterion should not be safety but rather whether the potential hazard of the recombinant DNA molecules differs significantly in degree or in kind from those found in nature or from biohazards that are successfully handled by conventional methods.

- That there is a question of quantification that goes beyond novelty; that is, a recombinational event that occurs very rarely in nature can be mimicked more frequently in the laboratory.

- That the PRG-RAC was ambiguous in describing the criteria to be used in judging novelty.

- That the list of nonnovel exchangers should not be limited to the exchange of chromosomal DNA, but should also include plasmid DNA exchange.

- That the list should not be drawn broadly at the species level, but should deal with exchange at subspecies levels.

- That footnote 1 of the PRG-RAC unjustly discriminated against natural recombinants involving eukaryotic viral DNA and other eukaryotic DNA. Others urged that this footnote be expanded to ensure that recombinants involving pathogenic bacteria not appear on the list.

- That experiments classified as P1+EK1 be exempted from the guidelines. Apparently harmless experiments do not warrant the administrative burden that accompanies inclusion within the guidelines.

- That it was unclear whether the PRG-RAC definition would permit "self-cloning" experiments (such as the cloning of *B. subtilis* genes in *B. subtilis*).

It proved impossible to reconcile these differences of opinion in the definition itself, but in my opinion the "Exemptions" section of the PRG-NIH as drafted does so successfully. This section was drafted by NIH staff in conjunction with a working group of the RAC; it was then modified slightly and endorsed by the full RAC at its meeting on April 27-28, 1978, and subsequently modified slightly for clarity by NIH staff. Before proceeding to a discussion of these exemp-

tions, however, I want to emphasize that no provision in this section may be cited to exempt from the guidelines an activity listed in the "Prohibitions" section.

The first exemption concerns recombinant DNA molecules that are not in organisms or viruses. This is in recognition that "naked" DNA, which is rapidly inactivated in nature, is extremely unlikely to be hazardous under experimental conditions. To guard against the remote possibility, however, that potentially harmful naked recombinant DNA will be incorporated into an organism, the handling of certain naked recombinant DNA molecules described in the "Prohibitions" section remains prohibited. It should also be noted that the concept of extremely low hazard of naked recombinant DNA was included in the PRG-RAC in the section on "Handling Recombinant DNA Molecules" at the end of part III. This language, I believe, is more appropriately presented under the "Exemptions" section.

The second exemption pertains to recombinant DNA molecules consisting entirely of DNA segments from a single nonchromosomal or viral source. This statement clarifies a category of "self-cloning" experiments that are considered safe enough to be excluded from the guidelines. This is a concept which the RAC tried to convey in the PRG-RAC definition by use of the phrase "different genomes," but which some commentators found ambiguous.

The third exemption concerns "self-cloning." It exempts from the guidelines recombinant DNA molecules made entirely from the DNA of a single organism including the plasmids, viruses, mitochondria, or chloroplasts indigenous to (i.e., found in nature in) that organism, when propagated only in that organism (or a closely related strain of the same species). This partially responds to the suggestion made by many commentators that experiments previously classified as P1+EK1 be excluded from the guidelines. It also covers some of the cases the RAC was including in the concepts of "novelty" and "different genomes." This exemption, however, does not include recombinant DNA molecules formed between viral DNA and eukaryotic host DNA. In this regard it is analogous to footnote 1 of the PRG-RAC.

The fourth exemption covers "certain specified recombinant DNA molecules that consist entirely of DNA segments from different species that exchange DNA by known physiological processes." In this case a list is prepared and periodically revised by the Director, NIH, on the recommendation of the RAC, after appropriate notice and opportunity for public comment.

This list is analogous to the list of "nonnovel exchangers" proposed in the PRG-RAC.

The initial entries on the list specified under exemption I-E-4 are given in appendix A to the guidelines. Any recombinant DNA molecules composed entirely of DNA segments coming from organisms listed in appendix A, would be exempt from the PRG-NIH under exemption I-E-4. The inclusion of the particular organisms listed in appendix A was recommended by the RAC at its meeting on April 27-28, 1978. (For further discussion of this list see appendix D to the accompanying Environmental Impact Assessment.)

The fifth exemption allows the Director, NIH, on the recommendation of the RAC, after appropriate notice and opportunity for public comment, to exempt other classes of recombinant DNA molecules if he finds that "they do not present a significant risk to health or the environment." The exemption of classes of experiments that do "not present a significant risk to health or the environment" is the language used in proposed legislation (H.R. 11192), recently reported out of the committee on Interstate and Foreign Commerce and the Committee on Science and Technology of the U.S. House of Representatives.

In addition to comments pertaining to the standards for exemption in the PRG-RAC, the following comments were directed toward the processes whereby exemptions would be made:

- Rather than compile a list of non-novel exchangers exempt from the guidelines, the burden of proof should be on the Director, NIH, to compile a list of novel exchangers which are subject to the guidelines.

- The procedures and criteria used in the development of the list should be explained thoroughly, and adequate opportunity should be given for public review and comment.

- Before being placed on the list, all the data pertaining to the application should be available for public review.

In response to these comments, the PRG-NIH specifies that for exemption I-E-4 and I-E-5—the two exemptions which involve the development of "lists"—these lists will be prepared by the Director, NIH, on the advice of the RAC, after appropriate notice and opportunity for public comment. Publication of the PRG-NIH includes appendix A giving an initial proposed list for exemption I-E-4. As part of the public comment which I am soliciting on the entire PRG-NIH, I include appendix A. In the future, no additions will be made to appendix A, nor will any items be listed as exemptions under exemption I-E-5, without ap-



propriate notice and opportunity for public comment.

#### *Prohibitions*

Two changes in this section have been initiated to make it more compatible with the new "Definition" and "Exemptions" sections. The first was to transfer this section from part III of the guidelines to part I. This is again to emphasize that the exemptions are not applicable to the six activities listed as being prohibited. The second was to drop all references to novel recombinant DNA's and natural genetic exchange. My other actions were based upon the following comments:

- There was general endorsement of the provision in this section which grants to the Director, NIH, upon the recommendation of the RAC, the authority to waive any of the prohibitions. The widespread support for this authority reflects the realization that many important risk-assessments experiments may not be able to proceed otherwise. NIH is now supporting and will continue to support experiments that will yield knowledge contributing to a better understanding of the nature of potential risks of recombinant DNA. This section has been expanded in the PRG-NIH to indicate that if any experiments are excepted from the prohibitions, they will "at that time be assigned appropriate levels of physical and biological containment."

- It was urged that the advice of other Government agencies, such as the Environmental Protection Agency (EPA) and the Occupational Safety and Health Administration (OSHA), should be sought when the Director, NIH, considers invoking this waiver authority. The Federal Interagency Committee on Recombinant DNA Research provides for coordination of policies in this area. EPA and OSHA are represented on the Committee. The advice of relevant research and regulatory agencies will continue to be sought when appropriate.

- It was suggested that the RAC as presently constituted should not be the sole advisory body because societal as well as scientific considerations must enter into the waiver decision. As explained in greater detail in part IV of this document, the membership of the RAC will be broadened modestly as needed for expertise, but provisions for public notice and opportunity to comment, and other appropriate administrative practices, can be used to ensure adequate public input when the issues warrant.

- It was suggested that an Environmental Impact Assessment or Statement should accompany each waiver. My waiver decisions will include a careful consideration of the potential

environmental impact, and certain decisions may be accompanied by a formal assessment or statement. This must be determined on a case-by-case basis.

- It was suggested that waiver of the prohibition on the large-scale use of culture containing recombinant DNA's be issued on the basis of industry's experience in dealing with such cultures. While such experience will surely be weighed in the decisionmaking, I believe that it should not be the sole criterion for granting such a waiver.

- Agricultural scientists noted the importance to their research community of being allowed eventually to release organisms containing recombinant DNA into the environment. When the original guidelines were presented to me in draft form in 1976, the release of organisms containing recombinant DNA molecules into the environment was to be allowed if a series of controlled tests had been done to leave no reasonable doubt of safety. At that time I rejected this waiver provision because of the limited scientific evidence available that any of the potential benefits from such a release were near realization.

The prohibition of deliberate release into the environment of recombinant DNA-containing organisms can be waived if all of the requirements for a waiver are met (and if the requirements of the National Environmental Policy Act are considered). Given the limited experience of NIH in agricultural research, the U.S. Department of Agriculture would be deeply involved in this process. I have given written notice of this opinion to the appropriate officials of the USDA.

- The Standing Advisory Committee on Recombinant DNA Research of the European Molecular Biology Organization (EMBO) has noted that the list of pathogenic organisms under prohibition I-D-1, especially those in class 5, may not be appropriate for all European countries, and that "the decision as to which pathogenic organisms should be classified as too dangerous to use must be the responsibility of national or regional authorities." In response to this a footnote could be added to the guidelines stating that prohibition I-D-1 relates only to research in the United States. I have decided, however, not to include such a footnote, because these guidelines are directed to NIH grantees and contractors, almost all within this country. In other countries, different criteria may govern.

- A final change in the PRG-NIH relates to prohibition I-D-1. As discussed below in this document in part III, considerable changes have been made in the sections dealing with the

use of viral DNA in recombinant DNA experiments. The history leading to these changes, including the report of the "Ascot" workshop (appearing as appendix E to the accompanying Environmental Impact Assessment) and the report of the working group held on April 6-7, 1978 (appearing as appendix F to the accompanying Environmental Impact Assessment), are discussed in detail in part III of this document under the heading "Recombinant DNA Experiments Involving Viral DNA."

One of the Working Group's recommendations, arising out of the "Ascot" report and endorsed by the RAC at its April 27-28, 1978, meeting and endorsed by me, is that the previous prohibition on the use in recombinant DNA experiments of Vesicular Stomatitis Virus (VSV) and of oncogenic viruses classified by the National Cancer Institute (NCI) as "moderate risk" should be lifted; instead, use of these viruses should be permitted under containment conditions to be specified in part III of the guidelines. The reasoning behind this is that recombinant DNA experiments with pieces of these viruses cloned in *E. coli* K-12 pose no more risk, and actually appear to pose clearly less risk, than work with the whole infectious virus itself. Since the Center for Disease Control (CDC) and NCI recommend that work with these whole viruses not be prohibited, but rather be performed under containment conditions similar to P3, there is no scientific reason to prohibit recombinant DNA work with these viruses.

Therefore, prohibition I-D-1 in the PRG-NIH no longer prohibits the use of VSV or oncogenic viruses classified by NCI as moderate risk; containment conditions for their use are specified in part III of the guidelines.

#### *General Definitions*

In response to commentators' suggestions that terms be more precisely defined, I have added a new section to the PRG-NIH with such definitions. Many of these terms are further discussed in part IV of PRG-NIH.

In summary, part I of the PRG-NIH has been extensively modified from that proposed in the PRG-RAC. In an effort to be responsive to the suggestions of commentators and to make the guidelines more comprehensible, the definition of recombinant DNA molecules has been simplified and clarified, the "Prohibitions" section has been transferred from part III to part I, and new sections have been added to part I including "Exemptions," part I, now entitled "Scope of the Guidelines," is composed of the following sections:

- Purpose
- Definition of Recombinant DN/ Molecules



- General Applicability
- Prohibitions
- Exemptions
- General Definitions

It should be noted that the Prohibitions appear before the Exemptions. This will again emphasize the fact that the latter provisions cannot be used to claim relief from the former.

## II. CONTAINMENT

The object of these revised guidelines is to insure that experimental DNA recombination will have no ill effects on the researchers, on the general public, or on the environment. The essence of their construction, as in the case of the 1976 Guidelines, is subdivision of potential experiments by class, and assignment to these of certain procedures for containment.

Containment is both physical and biological. *Physical* containment involves the isolation of the research by procedures that have evolved over many years of experience in laboratories studying infectious microorganisms. P1 containment—the first physical containment level—is that used in most routine bacteriology laboratories. P2 and P3 afford increasing isolation of the research from the environment. P4 represents the most extreme measures used for containing virulent pathogens, and permits no escape of contaminated air, wastes, or untreated materials. *Biological* containment is the use of biological agents that are crippled by mutation so as to be incapable of surviving under natural conditions.

### PHYSICAL CONTAINMENT

#### *Review of RAC-Proposed Guidelines*

Two major changes were proposed in the physical containment section of the PRG-RAC. One deals with the organization of the section; the other incorporates into the PRG-RAC the philosophy and guidance of the report of the NIH European Molecular Biology Organization (EMBO) Workshop on parameters of physical containment.<sup>3</sup>

Physical containment requirements for each P level have been organized under the topic headings *Laboratory Practices, Containment Equipment, and Special Laboratory Design*. This was done to emphasize the importance of laboratory practices and containment equipment in achieving the desired safety objective.

Other revisions contained in the "Physical Containment" section re-

fect a conscious effort to encourage international uniformity with respect to recombinant DNA guidelines. This has been achieved by revising the containment descriptions so that they are consistent with the guidance provided in the NIH/EMBO report. In addition, some statements have been rewritten and others added in order to clarify the basic requirements for each level of containment. The most significant clarifications were made in the areas on containment equipment and special facility design. The revisions, however, have not resulted in changing the purpose or intent of the physical containment descriptions in the 1976 Guidelines.

Two specific additions to the Guidelines that originated from the NIH/EMBO report are particularly notable. The first is that Tables I and II have been added to the P3 and P4 sections, respectively. These tables show combinations of safeguards that provide similar protection. The combinations are dependent on the level of biological containment. This approach allows flexibility in selecting containment equipment for a particular study without compromising safety.

The second specific addition is the inclusion of laboratory design criteria for an area in which personnel wear positive-pressure suits ventilated by life-support systems. This added approach provides a level of physical containment equivalent to that afforded by the glove-box cabinet requirement at the P4 level.

Other important changes are summarized below:

- Certain specific microbiological practices are mandated at the P1 level in the PRG-RAC (whereas in the 1976 Guidelines they were merely encouraged);
- At the P2 level, prohibitions against eating, drinking, smoking, and storage of foods have been extended from the work area to the entire laboratory;
- The universal biohazard sign is now required at the P2 level. Use of these signs has been extended to equipment such as freezers and refrigerators in which organisms containing recombinant DNA molecules are stored;
- Access procedures in controlled areas adjacent to P3 laboratories have been specified;
- Installation of foot-, elbow-, or automatically-operated facilities for washing hands is now required in P3-level laboratories;
- Specific guidance on containment equipment appropriate for laboratory animals has been added to the P3 and P4 sections;
- The labeling requirements for shipment of etiologic agents now apply to all organisms containing re-

combinant DNA molecules. Thus, the Center for Disease Control, U.S. Public Health Service, must be notified in the event of any accidental breakage during shipment. Also, agents requiring P4 containment must be packaged according to strict Federal standards and be shipped by registered mail or an equivalent system that provides for notifying the shipper upon delivery.

I have carefully reviewed the recommendations of the PRG-RAC relating to physical containment and propose to adopt them with certain modifications. The modifications, based on issues raised by the Director's Advisory Committee and public commentators, are discussed below.

#### *Review of comments and NIH-proposed guidelines*

As reported in the "Decision Document" which accompanied the release of the 1976 guidelines, comments on the containment provisions of the original Guidelines were directed to the definitions of both physical and biological containment and to the safety and effectiveness of the prescribed levels. Several commentators at that time found the concept of physical containment imprecise and subject to human error. Others questioned the concept of biological containment in terms of its safety and purported effectiveness in averting potential hazards. The commentators were divided on which method of containment would provide the most effective and safe system.

Several suggested that each of the physical levels be explained more fully. The physical containment section of the 1976 guidelines—and now of the PRG-NIH—is directly responsive to many of these commentators. In addition, the PRG-NIH takes into account the more recent comments related to standards for physical and biological containment. Commentators on the PRG-RAC have expressed particular concern over (1) the flexibility which allows various combinations of containment safeguards, (2) the design of containment systems, and (3) the adequacy of training in laboratory safety practices. The Standing Advisory Committee on Recombinant DNA Research of the European Molecular Biology Organization (EMBO) made a number of recommendations that NIH has considered, and public commentators have proffered additional suggestions relating to specific levels of physical containment and to shipment of recombinant DNA materials. These are examined below.

*Concept of "Flexibility."* Some commentators have expressed concern over the flexibility provided in Tables I and II that allows various combinations of containment safeguards. For

<sup>3</sup>The "Report of the NIH/EMBO Workshop (Parameters of Physical Containment)" may be obtained from the Office of Research Safety, National Cancer Institute, Room 3E47, Building 13, National Institutes of Health, 9000 Rockville Pike, Bethesda, Md. 20014.



example, some feel that work in a P3 facility conveys a desirable sense of hazard, whereas a reduction to the P2 level will promote an undesirable relaxation of vigilance. It has also been suggested that an increase in the options increases the difficulty of control and implementation of the guidelines. Some commentators object to specific options provided at the P3 and P4 levels. NIH has been urged to include a better explanation of the rationale for this flexibility.

Indeed, the calculus of switching physical and biological containment levels has been questioned. Does an increase in biological containment from EK1 to EK2 truly compensate a reduction in physical containment from P3 to P2?

The scale of either form of containment from least to greatest is not necessarily linear, and substitutions are only roughly approximate. Nevertheless, there are some numerical bases for comparison.

For example, a class III biological safety cabinet is required at the P4 level (if a positive pressure suit is not used); whereas at P3, one can work in an open-front biological safety cabinet. The class III cabinet is virtually an absolute containment system. It is certified gas-tight when tested under positive pressure. It is operated under negative pressure to gain optimum safety. It provides at least a 10,000- to 100,000-fold increase in safety over that provided by a Class I or II cabinet, which is required at the P3 level.

The relative safety of these two containment cabinets is based on the efficiency of their exhaust-air treatment systems. The exhaust-air treatment for the class III cabinet is provided by two HEPA filters installed in series. This arrangement gives a containment efficiency of at least 99.99 percent. The exhaust-air treatment for class I and II cabinets, with only one HEPA filter, provides a containment efficiency of 99.99 percent. The potential for escape of microorganisms across the open front of the class I and II cabinets is similar to that for escape through the exhaust-air treatment system under operating conditions. These cabinets must meet a performance criterion which permits fewer than 20 microorganisms to escape through the open front when  $1 \times 10^6$  (100,000,000) to  $8 \times 10^6$  (800,000,000) microorganisms are experimentally released within the cabinet. The degree of protection provided by the class I or II cabinets is equivalent to the increase in safety at the P3 level over that provided at the P1 level which allows open-bench operations.

The symbol HV (Host-Vector) is used in the PRG-NIH to designate biological containment systems encompassing the present EK systems. HV2

is defined in terms of a probability of escape of recombinant DNA of less than 1 in  $10^6$  (1 in 100,000,000). In considering "equivalency" between P and EK levels, it is recognized that the two systems are conceptually different. Biological safety cabinets are designed primarily for the protection of the laboratory worker, and all physical containment protection stops at the walls of the laboratory. Biological containment continues to operate even were an organism to escape from the laboratory.

The flexibility allowed in alternate P and HV levels is carefully explained in the text of the PRG-NIH, and the investigator must follow the explicit requirements set forth in Part III of the proposed guidelines and Tables I and II.

**Redundancy.** A question has been raised concerning redundancy in the safety systems to insure that alternate systems will come into play in case of an emergency—for example, power failures or major accidents. The concept of redundancy is inherent in the design of the containment systems used in recombinant DNA research. Redundancy, however, is provided by standby systems, but rather by design features and operational requirements of the safety systems used. For example, primary containment at the P4 level is provided by the gas-tight class III cabinet system. These cabinets are also maintained under negative air pressure, which would provide protection against the release of microorganisms in the event that a glove were to rupture or a leak to develop. Similarly, the physical isolation of the class III cabinet would not be compromised in the event of a power failure. However, since the redundant protection provided by the negative pressure would be compromised, personnel would be instructed to stop work immediately during the power interruption. Another example is the requirement that the exhaust and supply fans for P4 facilities be interlocked. This assures that in the event of failure of the exhaust fan, the supply fan will automatically shut down, preventing the pressurization of the laboratory environment. As with the class III cabinet example, personnel would stop their work because of the loss of secondary protection provided by the ventilation systems. Operational procedures, therefore, become an important element in assuring safety in the event of any system failure.

Institutions are required to devise emergency plans to handle possible problems. In response to recommendations of the Environmental Protection Agency Study Group on Recombinant DNA and to concerns raised by commentators, NIH has stipulated more clearly (in the supplement to the

PRG-NIH entitled, "Laboratory Safety Monograph") certain elements in these emergency plans. Moreover, NIH staff have recently met with representatives of the center for Disease Control (CDC) to establish a mechanism for providing advice, consultation, or assistance, if necessary, in case of an emergency, such as an accident in the laboratory.

**Laboratory safety.** A number of commentators felt that the PRG-RAC was vague in regard to the training in safety of researchers, students, and janitors. It was urged that specific curricula be developed and that a requirement for certification of training be stipulated in the guidelines (a recommendation also made by the EPA Study Group on Recombinant DNA). It has been suggested, further, that NIH develop curricula for training.

At the present time, NIH has a contract with the American Society for Microbiology (ASM) to develop minimum standards for training participants in recombinant DNA research. The ASM Working Panel will consider what standards of training in microbiologic techniques are appropriate for the conduct of experiment requiring P1 through P3 containment conditions. The Panel will solicit views from the scientific community to develop minimum requirements for training. The Panel's report will be made available to the IBC's and investigators to set standards for all who participate in this research. In view of these developments, formal certification requirements by NIH are considered premature.

Other commentators stressed the need for more stringent measures in regard to safe practices. In particular, these commentators urged regular monitoring of laboratory facilities, preferably at all P levels. This would include monitoring of microbiological practices, serological monitoring, and CDC review of incidence of infections. It was also suggested that regular inspections be performed by individuals not associated with the institution (to preclude conflict of interest); that the guidelines require a member of the work force to be represented on the institutional biosafety committee; and that penalties (other than cutoff of funds) be imposed on violators as a deterrent. I have accepted many of these proposals; the specific NIH actions in regard to them are discussed in Part IV of this document.

Appendix D, "Supplementary Information on Physical Containment," was added to the 1976 guidelines in response to numerous requests for greater specificity in describing containment requirements. Commentators noted the absence of this document from the PRG-RAC and urged that it be retained and further expanded. Ac-



cordingly, a special committee of safety and health experts was convened by W. Emmett Barkley, Ph. D., Director of the Office of Research Safety, National Cancer Institute, to review and revise this supplementary information. Several sections have been extensively rewritten, and new sections have been added on evaluation methods for P3 facilities, certification procedures for P4 facilities, certification of biological safety cabinets, emergency control procedures, medical surveillance programs, and other topics. This document is separately available as "Laboratory Safety Monograph—A Supplement to the NIH Guidelines for Recombinant DNA Research."

*Other comments.* A number of additional comments have been received from public commentators relating to proposed actions at specific levels of physical containment.

It has been suggested that certain requirements at the P1 level remain "permissive" rather than be changed to "mandatory"; i.e., that the language in the PRG-NIH read "should" rather than "shall." NIH considers this inconsistent with the stated principle of specifying requirements, and has therefore mandated adherence to these good microbiological practices.

The EMBO Standing Advisory Committee on Recombinant DNA Research has recommended that simple air exhaust cabinets be used at the P1 level when there is likelihood of producing large amounts of aerosols. In the view of NIH such cabinets are unnecessary, as the agents used at this level would not create aerosols hazardous to laboratory workers.

A recommendation has been received from the EMBO Standing Advisory Committee on Recombinant DNA Research to reclassify P2 with a class III cabinet as equivalent to P3 specifications. While this option was permitted in the 1976 guidelines, it is no longer considered practical. The cost of fabricating and installing class III cabinets would far exceed the cost of installing a new exhaust-air system for the laboratory. It is considered more cost-effective and desirable to convert P2 laboratories into P3 laboratories. The elimination of the 1976 option should be viewed as an encouragement to upgrade laboratories.

It has been observed that many class II safety cabinets do not meet accepted standards. A recommendation has been made that the local IBC be authorized to certify these cabinets, and that such a requirement be included in the guidelines. It should be noted that the guidelines already authorize IBC's to certify safety practices and procedures; however, to respond more directly to the above suggestion, a special section on certification of biological

safety cabinets has been included in the supplement to the PRG-NIH entitled "Laboratory Safety Monograph."

The EMBO Standing Advisory Committee on Recombinant DNA Research observes that in the case of a P3 facility, the proposed revisions do not speak to precautions against the contamination of the main water supplies by laboratory water systems. It is noted that building codes and laboratory design standards require that precautionary measures be taken to separate potable water systems from laboratory process water. Additional precautions have been required at the P4 level. Standard design practice is felt to be appropriate at the P3 level.

Some commentators have pointed out that the PRG-RAC did not require an autoclave in the P3 laboratory itself, but only within the building. The 1976 guidelines require that for P3 laboratories an autoclave be available "within the building and preferably within the controlled laboratory area." Some believe an autoclave in the P3 laboratory should be required. One commentator felt that the autoclave should be "as close as possible" to the controlled area of the P3 laboratory, not merely available in the same building. He pointed out that from an operational point of view, the closer the autoclave can be to the solid waste, the better. This is especially true in the larger medical research complexes, where transport of wastes from the laboratory to the autoclave might involve passage "via some rather sensitive patient areas of the institution." He prefers that the autoclave be located either in the controlled area or as close to it as possible, with such explicit language in the guidelines. The language in the 1976 guidelines stating that in a P3 laboratory "an autoclave shall be available within the building and preferably within the controlled laboratory area" has been reinserted in the PRG-NIH. However, an absolute requirement that the autoclave must be within the controlled area is not considered appropriate, since contaminated materials can be safely transported. Such a requirement would exclude the use of autoclaves in waste staging areas that have been conveniently sited to support an entire facility.

The PRG-RAC states that P4 work can be done in either (1) a class III cabinet system or (2) a class I or class II cabinet system in a special area where all personnel wear one-piece, positive-pressure suits. Some investigators apparently prefer use of pressure suits over work in the class III cabinets. NIH believes that the suits are especially useful in working with experimental animals in a P4 facility or with large amounts of material. At

present, however, most recombinant DNA studies are handled more practically in a class III without need for a suit.

In 1976, several commentators advocated that NIH arrange for sharing of P4 facilities, both by investigators from the NIH intramural program and from institutions supported through NIH awards. In response to these suggestions and those of recent commentators, we have arranged to make our recently established P4 facilities at the Frederick Cancer Research Center (Fort Detrick) available to outside scientists.

*Shipment.* Some commentators have urged that stricter controls be required on shipping recombinant DNA molecules in or out of the country. It has been recommended, for example, that shipping procedures differentiate between types of substances being transported. We wish to emphasize that requirements for shipping organisms that contain recombinant DNA molecules are consistent with relevant Public Health Service, Department of Transportation, and Civil Aeronautics Board regulations, and are also in compliance with the World Health Organization recommendations on the international shipment of biologic agents. It should be noted that organisms containing recombinant DNA molecules all require the same containment conditions as for the most hazardous known agents.

The EMBO Standing Advisory Committee on Recombinant DNA Research recommends that before a shipment is made, the recipients of organisms containing recombinant DNA molecules should affirm to the donors that they are following the safety standards and practices of their country. NIH considers this a sound recommendation and requires the following (as stated in the NIH Guide for grants and contracts):

All memoranda of understanding and agreement (MOA's) submitted with competing and noncompeting applications involving recombinant DNA research must indicate that the principal investigator (program director, fellow, or candidate) agrees to comply with the NIH Guidelines and other specific NIH instructions pertaining to the proposed project. Included in the provisions are the following pertaining to shipment or transfer of recombinant DNA materials:

A. Prior to shipment or transfer of recombinant DNA materials to other Federally funded investigators within the United States, the sending laboratory shall obtain a letter from the requesting laboratory stating that:

1. Research involving recombinant DNA molecules shall be conducted in compliance with the NIH Guidelines and other NIH instructions, and that the requesting laboratory shall not transfer the recombinant DNA materials to other laboratories;

2. The requesting laboratory has been reviewed by its Institutional Biosafety Com-



mittee which has certified that facilities, procedures, and the training and expertise of the personnel involved are adequate;

3. An approve MUA with a certification is on file with the funding agency of the requesting laboratory;

4. A copy of this letter is on file with the requesting laboratory's Institutional Biohazards Committee.

B. Prior to shipment or transfer of recombinant DNA materials to non-Federally funded investigators or institutions within the United States, the sending laboratory shall obtain a letter from the requesting laboratory stating items 1, 2, and 4 under A above.

C. Prior to international shipment of recombinant DNA materials, the sending laboratory shall obtain a statement from the requesting laboratory stating that research involving recombinant DNA molecules shall be conducted in accordance with the containment levels specified by the NIH Guidelines, or applicable national guidelines if such have been adopted by the country in which the research is to be conducted, and that the requesting laboratory shall not transfer the recombinant DNA material to other laboratories.

D. The sending laboratory shall maintain a record of all shipments of recombinant DNA materials and shall provide NIH with a complete list of such shipments in the annual progress report for NIH grants and contracts.

**Mouth-pipetting at the P1 level.** Both the 1976 guidelines and the PRG-RAC prohibit mouth-pipetting at the P2, P3, and P4 levels. For the P1 level, however, they state, "Although pipetting by mouth is permitted, it is preferable that mechanical pipetting devices be used. When pipetting by mouth, cotton-plugged pipettes shall be employed." A number of commentators have urged that mouth-pipetting be prohibited at the P1 level of physical containment. This is strongly endorsed by NIH safety experts, who point out that this is an important safety feature, and that efficient new mechanical pipetting aids should not greatly hamper researchers. Also, the EMBO Standing Advisory Committee on Recombinant DNA Research "believes that mouth pipetting should be prohibited in the P1 laboratory, as it is prohibited in P2-P4 laboratories." In addition, the Working Group of American virologists which met on April 6-7, 1978, to review the report of the U.S.-EMBO Workshop to Assess Risks for Recombinant Experiments Involving the Genomes of Animal, Plant, and Insect Viruses<sup>1</sup> wrote the following in their report:

In its deliberations, the Working Group was impressed with the safeguards afforded by a ban on mouth pipetting for recombinant

ant DNA experiments involving *E. coli* K-12 host-vectors. The group felt that the only plausible way *E. coli* K-12 could gain entry into laboratory workers was by oral ingestion. The analysis contained in the U.S.-EMBO Report was predicated on the remote possibility that *E. coli* K-12, containing eukaryotic viral DNA, would be swallowed and the viral DNA insert would be delivered to a tissue in the body which ordinarily would be inaccessible to the virus. A prohibition of mouth pipetting would clearly prevent this sequence of events from even beginning. The Working Group therefore recommended that no mouth pipetting be allowed at any level of physical containment (including P1) when working with *E. coli* K-12.

On the other hand, when I requested that the RAC, at their April 27-28, 1978, meeting reconsider whether mouth pipetting should not be banned at the P1 level, it was their consensus that many experiments classified as P1 need not include a ban on mouth-pipetting, and that therefore P1 in general should not be redefined. Instead, they recommended that only certain classes of P1 experiments be designated as requiring no mouth-pipetting.

In resolving this issue, I have decided to adopt the conservative position and ban mouth-pipetting. Accordingly, language has been inserted in the PRG-NIH saying that at the P1 level, "Mechanical pipetting devices shall be used; pipetting by mouth is prohibited." Since mouth-pipetting had already been banned at the P2-P4 levels, this means that it is now banned for all experiments covered by these guidelines.

#### BIOLOGICAL CONTAINMENT

##### Review of RAC-proposed guidelines

Experiments on recombinant DNA's by their very nature lend themselves to applications of highly specific biological barriers as a means of containment. In fact, there are natural barriers that limit either the infectivity of a vector or vehicle (plasmid or virus) to specific hosts, or its dissemination and survival in the environment. Both the vectors whereby DNA is transferred to the recipient host and the host cells wherein it replicates can be designed genetically to decrease by many orders of magnitude the probability of dissemination of recombinant DNA outside the laboratory.

The proposed revised guidelines describe the categories of hosts and vectors to be used in minimizing the spread of organisms containing recombinant DNA. The PRG-RAC differs in some respects from the 1976 guidelines as a result of certain changes in definitions of HV systems and in the requirements at specific HV levels (notably HV3). A new section has been added on certification of host-vector systems.

**Definitions of host-vector systems.** A new nomenclature—HV1, HV2, and HV3—has been developed to incorporate a variety of hosts and vectors into the framework initially established for *E. coli* K-12. In particular, the PRG-RAC provides criteria for HV1 systems other than *E. coli* K-12. In the 1976 guidelines, cloning systems other than *E. coli* K-12 were to be considered only if superior to *E. coli* K-12 in containment properties; but it is now recognized that many useful experiments can only be conducted using HV systems other than those based on *E. coli* K-12, and that such experiments should be permitted so long as the proposed HV system provides equivalent biological containment. The new HV1 criteria provide a structure for approval of systems that meet these requirements.<sup>3</sup>

**HV2 systems.** At the HV2 level of containment, there are no substantive changes comparing the 1976 guidelines with the PRG RAC. However, the RAC, on June 23, 1977, the same day it approved the PRG-RAC—also adopted unanimously "Instructions to Investigators Concerning Data To Be Submitted on Host-Plasmid Systems Proposed for EK2 Certification." Although not officially part of the PRG-RAC, these instructions set forth criteria that any putative EK2 host-vector systems must meet before recommendation by the RAC for certification. The RAC applied these criteria in reviewing new systems (pBR322 and pBR313 in x1776) at the June 23, 1977, meeting, and will do so for all future submissions. It was made clear at the meeting that these criteria are definitely more stringent than previous ones, and this greater stringency means that EK2 host-vector systems approved now and to be approved in the future are even safer than those approved previously.

**Requirements for HV3 systems.** These have been made more stringent in the PRG-RAC than the corresponding requirements for EK3 in the 1976 guidelines. The PRG-RAC requires that the vector be dependent on its propagation host or be highly defective in mobilizability. "Reversion to host-independence must be less than 1/10<sup>6</sup> per vector genome per generation." Also, the vector may carry no resistance to antibiotics used clinically or in agriculture. The provision that antibiotic resistance markers of medical or agricultural importance are not to be used in the vector should prevent any inadvertent advantage for recombinant DNA-bearing vectors that encounter antibiotics in the environment.

<sup>3</sup>Under the proposed revisions, HV1s other than *E. coli* K-12 need not offer a distinct advantage over *E. coli* K-12 host-vectors, need not be capable of modification to HV2 and HV3, and need not be class I etiologic agents.

<sup>1</sup>The history of the U.S.-EMBO Workshop and the April 6-7, 1978, working group is discussed in detail in Pt. III of this document under the heading "Recombinant DNA Experiments Involving Viral DNA" and the report of the working group appears as App. E to the accompanying environmental impact assessment.



**Certification of host-vector systems.** A new section has been added detailing the responsibility for certification of HV1, HV2, and HV3 systems, the types of data to be submitted, and the mechanisms for distributing strains once certified. The section delineates procedures used by the RAC for the past 2 years and therefore represents no change from practices under the 1976 guidelines.

**Review of comments and NIH-proposed guidelines**

I have reviewed the biological containment section of the PRG-RAC in the light of comments and suggestions made by participants of the Director's Advisory Committee (DAC) as well as written comments received before and afterward, and have adopted the recommendations of the PRG-RAC with some revisions. An analysis of the specific issues raised by commentators and the basis for my decision follow.

**Development of Alternative Host-Vector Systems.** Many commentators from the scientific community believe that the PRG-RAC discriminates against alternate host-vector systems other than *E. coli* K-12. They urge development of other systems, maintaining that new systems will be needed increasingly, both in pure research and in industry, and should be certified as soon as possible. It is unlikely, according to one commentator, that agriculture will best be served through the use of *E. coli* K-12 (or *B. subtilis*), and that alternate host-vector systems are therefore essential if the potential of recombinant DNA technology for agriculture is to be realized. In view of the support evident at the 1976 DAC meeting for NIH to encourage development of alternate host-vector systems, one commentator expressed disappointment that there was not now a large NIH contract program in this area.

Others view the introduction of alternate HV systems with some misgivings. It was pointed out, for example, that if uncertainty continues to surround research with so well-studied an organism as *E. coli* K-12, our ignorance must be that much greater with regard to any other organism—its ecological involvement, the organisms with which it can exchange DNA, etc. Moreover, the guidelines, which have been developed around the use of *E. coli* K-12, are primarily focused on dangers to man, and the introduction of new systems may affect other life forms with which we should be equally concerned. In the view of commentators who urge restraint, the larger the number of systems certified, the greater the problem of monitoring the work.

Clearly, however, research addressed to the development of other host-vector systems must proceed. This is

particularly evident in the agricultural sector, where the potential for immediate benefits to man is great. At present, a number of alternate systems, including those using *B. subtilis* and *Saccharomyces cerevisiae*, are being developed by NIH grantees. The interest shown by numerous investigators in developing new host-vector systems means that NIH need not develop a special program to promote research in this area.

I appreciate and understand the concern of those who urge deliberate caution. I would stress that the same considerations of safety and risk associated with the use of *E. coli* K-12 will also apply to any new host-vector systems to be certified in the future.

**Risk Assessment.** Many commentators advocate more studies in risk assessment. It has been maintained that assumptions about biological containment may not be valid and that all components should be tested. Concern has been expressed that the biological containment safety systems may fail altogether.

Some risk assessment studies are prohibited by the 1976 guidelines. Under the PRG-RAC, however, the Director, NIH, on recommendation of the RAC, would have discretion to permit such risk assessment experiments by granting a waiver from a specific prohibition. There was virtually unanimous support for this discretion at the DAC hearing in December 1977. Of course, its exercise must be consistent with standards of due process for the scientific community and the public.

Risk assessment studies are proceeding both within and outside the United States. For example, the "polyoma" experiment, which was delayed in this country because of litigation and the renovations necessary to meet the extremely stringent P4 requirements, has now begun here, and a similar experiment is proceeding in Europe. The work of Robin Holliday in assessing statistical probabilities of biological accidents is also noteworthy (see appendix P of the October 1977 Environmental Impact Statement).

NIH is committed to the conduct and support of risk analysis studies to determine the extent to which certain potentially harmful effects from recombinant DNA molecules may occur. It is intended that the NIH P4 facilities both in Bethesda, Md., and at the Frederick Cancer Research Center will serve as a focal point for many such

"Two NIH virologists, Drs. Wallace Rowe and Malcolm Martin, are linking viral DNA from the mouse polyoma virus with the DNA of bacterial plasmids and bacteriophages and inserting this recombinant DNA into a weakened strain of *E. coli*. The bacteria will then be injected into or fed to mice to determine the effects, if any, of the viral DNA.

studies. Provision has already been made to share these facilities with non-governmental scientists.

It should be stressed that prior to certification as EK2, each candidate EK2 host-vector system is analyzed in great detail by the RAC and NIH. Much data must be submitted, a good deal of which is risk assessment data.

**Safety of *E. coli* K-12.** In 1976, there was considerable comment regarding the use of *E. coli* K-12 as a host, including recommendations that its use be prohibited. Some recent commentators have also questioned the safety of *E. coli* K-12, noting that the Falmouth Workshop proceedings had not been published for public review. On the other hand, one commentator urged that, base on the safety of *E. coli* K-12, essentially all experiments employing *E. coli* K-12, be exempted from the Guidelines. An extensive discussion of *E. coli* K-12 together with new scientific information on its safety are presented in part III of this document and in a special section of the Environmental Impact Assessment.

The proceedings of the Falmouth Workshop have now been published in the May 1978 issue of *Journal of Infectious Diseases*. Reprints are available from the Office of Recombinant DNA Activities, NIH, Bethesda, Md. 20014. As noted in a letter of July 14, 1977, from Dr. Sherwood Gorbach, moderator of the Falmouth Workshop and Chief of Infectious Disease and Professor of Medicine at Tufts University School of Medicine, "The participants arrived at unanimous agreement that *E. coli* K-12 cannot be converted into an epidemic pathogen by laboratory manipulations with DNA inserts."

**Comments on Specific Containment Levels.** One commentator sought clarification of section II-D-1-a of the PRG-RAC, which defines HV1. According to the second sentence, "The host should have a low potential for survival in its natural environment." As the commentator noted, "'natural environment' could be ambiguous, in practice. Presumably many of the host cells that people may wish to use have no natural environment other than the laboratory." I referred this comment to the RAC at its April 27-28, 1978, meeting. The RAC agreed that this sentence is ambiguous and recommended that it be deleted. I have done so in the PRG-NIH.

A question was raised on whether HV1 hosts could be wild type organisms or if they are always "meant to harbor containment mutations." If wild type organisms can qualify as HV1, then the definition of HV1 should be reworded to state this explicitly. The answer to the question is that if wild type organisms meet the criteria for HV1, they may be certified



as HV1. However, I see no need to modify the definition to state this explicitly.

One commentator thought the standards for HV1 should be significantly relaxed and that NIH approval should not be necessary. He proposed that the Guidelines state that "wild type isolets of any bacterial species not known to be pathogenic to humans, to domestic animals, or to agriculturally important plants may be used as an HV1 host-vector system, provided that all components of recombinant DNA molecules introduced into such a host-vector system, are derived from other prokaryotic organisms within Etiologic Agent Class 1." I have rejected this suggestion since I believe it prudent, at least for the present, to have higher standards and to require NIH approval before a system may be called HV1. Some commentators have urged that the requirement for independent confirmation of relevant phenotypic and genotypic traits before certification at the HV3 level should also be applied at the HV2 level. There are two objects of such testing: (1) To determine whether a system already approved has changed its characteristics before a new sample of it is distributed (for example, whether the amber mutations for phage systems are still present), and (2) to repeat independently all the safety tests required before each new system would be certified. The first could be done easily and is sufficient to confirm the safety characteristics; the second is cumbersome and difficult. It should be pointed out that the RAC and its working groups that review the data on proposed HV2 systems are, in effect, conducting an independent check and know this area of research well. Further, the Committee may request that additional experimental data be submitted as part of its review. NIH believes these controls to be sufficient. Consequently, the requirement for an independent check at the HV2 level is deemed unnecessary.

For the HV3 level of containment, some objections have been raised to the requirement banning antibiotic-resistance markers. Antibiotic resistance can serve as a valuable marker in experiments with organisms bearing recombinant DNA. The ban at the HV3 level, however, is prudent inasmuch as organisms rendered antibiotic resistant would be less amenable to control should they escape from the laboratory. This requirement also allows only a certain class of certified HV2 systems to qualify for HV3. Therefore, attempts to develop systems that meet these HV3 criteria should simultaneously upgrade the HV2 systems in use, since it is to the experimenter's advantage to use those HV2 systems

with the greatest likelihood of meeting HV3 criteria.

**Certification.** A number of commentators have urged more precise criteria for biological containment systems. They feel that criteria should be as objective as possible and should be framed in terms of performance, as in the case of physical containment (for example, safety cabinets). It should be stressed that specific objective criteria do exist for EK2 host-vector systems. These, however, do not appear in the Guidelines themselves, but rather as information in the Environmental Impact Statement, Appendix H, entitled "Certification of EK2 Host-Vector Systems." To insure that detailed material on certification of host-vector systems is readily accessible, NIH will publish specific criteria in a standardized format in the *Recombinant DNA Technical Bulletin*. Specific instructions concerning the type of data to be submitted to NIH for proposed EK2 systems involving either plasmids or bacteriophage lambda in *E. coli* K-12 are available from the NIH Office of Recombinant DNA Activities, and a statement to this effect is included in the PRG-NIH.

Many problems persist for setting general criteria that could be applied to all organisms for possible certification as HV2 and HV3. For example, with *B. subtilis*, which forms spores, safety would depend on nonsporulating derivatives. Some commentators urged that all new systems be certified with deliberate caution, and that criteria and evidence should be a matter of public record before decisions are made. The *B. subtilis* system was cited as a case in point; extensive public analysis and debate should precede certification.

I agree that prior notification to the public in the *FEDERAL REGISTER* should be given when the RAC considers applications for certification. (It should be noted that all meetings of the RAC are announced in the *FEDERAL REGISTER*.) I also agree with the suggestion that the RAC should have a more fixed schedule of meetings throughout the year so that the public and scientific communities may know the schedule of events clearly.

The entire section (II-D-2-a) on responsibility for certification of host-vector systems has been rewritten in the PRG-NIH to clarify this process.

**Distribution of Certified Host-Vectors.** Some commentators have suggested that NIH distribute HV1 systems as well as HV2 and HV3 systems. Language has been placed in the PRG-NIH indicating that, where appropriate, HV1 systems other than *E. coli* K-12 may be sent by NIH to investigators.

Concern has been expressed about culture contamination and how this

problem would be addressed. The PRG-NIH provides that if NIH propagates any of the host strains or phages, it will not distribute the culture before sending a sample to the investigator who developed the system or to an appropriate contractor for verification that "the material is free from contamination and unchanged in phenotypic properties." The PRG-NIH also assigns to the investigator the responsibility for "insuring the integrity of physical containment (e.g., biological safety cabinets) and biological containment (e.g., genotypic and phenotypic characteristics, purity, etc.)."

Distribution of certified host-vector systems has raised comment relating to the protection of proprietary information and patent rights, for this section of the Guidelines seems to mandate distribution and might conflict with patent protection. NIH has carefully considered such protection. Language has been included in the PRG-NIH (in section IV-C) allowing RAC review for certification at the request of the private sector. The language notes, however, that interested individuals should consider filing for patent protection before submitting information to DREW. To be consistent with the institutional patent agreement policies of the Department of Health, Education, and Welfare, support is accorded the concept of protection of proprietary and patent rights within the bounds of due process for public review.

### III. CONTAINMENT GUIDELINES FOR COVERED EXPERIMENTS

#### REVIEW OF RAC-PROPOSED GUIDELINES

A major concern of all individuals who have participated in establishing guidelines for recombinant DNA research is that any guidelines that are drafted and adopted be reassessed periodically and changes made when warranted by new information and/or experimental data. In keeping with this responsibility, the RAC compiled additional information pertaining to risk assessment in recombinant DNA research. This information is in the following forms:

1. Consultations with scientists with expertise in the areas of evolution, plant biology, bacteriology, virology, and human and animal infectious diseases;

2. Reports from scientific meetings dealing with the potential biohazards of recombinant DNA research (for example, the *Tenth Miles International Symposium on Recombinant Molecules—Impact on Science and Society*, Cambridge, Mass., June 1976; the *National Academy of Sciences Forum on Recombinant DNA Research*, Washington, D.C., March 1977; *Genetic Engineering for Nitrogen Fixation*, Brook-



haven, N.Y., March 1977; and the *Workshop on Studies for Assessment of Potential Risk Associated with Recombinant DNA Experimentation*, Falmouth, Mass., June 1977;

3. Results from experiments specifically designed to test (a) the survivability and colonizing ability of *E. coli* K-12 and EK2 host-vector systems, (b) the transmissibility of plasmids and phage vectors, (c) the potential of *E. coli* K-12 for pathogenicity, and (d) the potential of genetic exchange between diverse bacteria and between eukaryotic and prokaryotic organisms.

Each category of experiments in part III of the original guidelines was then extensively examined, applying the following criteria to the new information:

- The degree to which the DNA segment has been purified away from other genes and shown to be free of harmful characteristics;
- The potential biohazard associated with the DNA of the cell or microorganism that serves as the DNA source (e.g., genes for toxin production);
- The potential biohazard associated with the vector that serves to transmit the source DNA to a recipient host cell;
- The ability of the vector to survive in natural environments or habitats;
- The kinds and number of different organisms that are susceptible to infection by the vector or recipient;
- The potential biohazard of the recipient host cell that serves to replicate the recombinant DNA molecule;
- The ability of the recipient cell to survive in natural environments of habitats;
- The ability of the recipient cell to transmit the recombinant DNA molecule to other cells capable of surviving in natural environments or habitats;
- The potential of the recipient cell to obtain the source DNA by natural means; and
- The evolutionary relatedness of the DNA source to humans. The potential dangers are considered to increase as the organism providing the source DNA approaches humans phylogenetically. Thus, source DNA from primate cells is considered to have greater potential danger than source DNA from prokaryotes.

To present more clearly the changes in containment levels proposed by the PRG-RAC, a table was prepared for use at the December 1977 meeting of the Advisory Committee to the Director, which compared the containment levels in the PRG-RAC with those of the 1976 guidelines. This table has now been expanded with a third column to show the containment levels of the proposed revised guide-

lines which are now being proposed by NIH (called PRG-NIH). The table appears as appendix A to the accompanying Environmental Impact Assessment.

The remainder of this section summarizes a number of the proposed changes comparing the 1976 guidelines with the PRG-RAC. (Not all the changes are discussed here; certain items in which the PRG-NIH differs significantly from the PRG-RAC are considered below in the section entitled "Review of Comments and NIH Proposed Guidelines.") The numbers in parentheses indicated the line numbers on the table to which the proposed revision applies.

The principal changes reflected in the table are as follows:

- Several categories of experiments (primarily those involving prokaryotes that are exchangers of genetic information with *E. coli* in nature) are no longer subject to the provisions of the PRG-RAC due to the changes in the definition. (See lines 20, 21, 27, 46, and 47.)
- Shotgun experiments involving birds and mammals other than primates were the subject of lowering of containment from P3+EK2 to P2+EK2. This action reflects the increased confidence of the RAC in the EK2 host-vector systems. (See lines 4 and 5.)
- Another category which the RAC decided was in need of revision was that pertaining to the cloning of DNA from organisms producing a toxic product. This was clarified in the PRG-RAC by specifying whether or not polypeptide toxins are produced, and setting containment levels accordingly. Polypeptide toxins are specified, since they might be encoded by a single gene or cluster of genes. Toxins of other chemical structure would not result from a single gene or cluster of genes. (See lines 8, 9, 10, 11, 12, 16, 17, and 19.)
- For several categories of experiments, it is proposed that the investigator have the option of working at P2+EK1 or P1+EK2 rather than the P2+EK1 levels previously specified. This again reflects confidence in the EK2 systems. (See lines 7, 14, and 15.)
- The lowering of containment for experiments with rigorously characterized clones free of harmful genes was revised to provide more flexibility. Under the PRG-RAC, institutional biosafety committees (IBC's) would be able to lower containment by a single level. The IBC should consider the purity, extent of characterization, and harmlessness of the clone before allowing such lowering. Reduction of containment by more than one level would require approval by NIH. Under the 1976 guidelines, NIH had the option of lowering containment down

to certain specified levels or not lowering it at all. The PRG-RAC would allow NIH to consider all available data for the clone and to lower containment accordingly.

In addition, the section now applies to rigorously characterized clones from any permissible experiment in *E. coli* K-12. Under the original guidelines, containment for *E. coli* K-12 clones containing characterized and harmless portion of viruses and plasmids could not be lowered.

The rationale for these proposed changes is explained in further detail in the Environmental Impact Assessment.

#### REVIEW OF COMMENTS AND NIH PROPOSED GUIDELINES (GENERAL)

##### Rationale

Part III of the guidelines received the most extensive comment of any section during the development of the original guidelines in early 1976. While there was also much discussion of this part in the PRG-RAC, the issues raised did not primarily address the proposed changes in the containment levels but more general topics such as the need for a rationale for each of the changes.

A number of commentators asked that the rationale for the classification of permissible experiments be clearly spelled out. It was pointed out that (1) the part on permissible experiments is especially difficult for a lay person to understand, (2) the whole categorization is dependent upon investigational confidence rather than documented fact, and (3) the quantification of containment levels, the means by which the levels were decided, and the rationale for raising and lowering these levels are not clear.

In general, the classification may appear somewhat arbitrary, because it depends in large part on the scientific judgment of the RAC rather than on demonstrable risk, since there is actually no scientific evidence of hazard in any recombinant DNA experiment.

The rationale for classifying different recombinant DNA experiments at different containment levels was explained in the "Decision of the Director, National Institutes of Health, To Release Guidelines for Research on Recombinant DNA Molecules," which was published along with the current guidelines in the FEDERAL REGISTER on July 7, 1976, as follows:

The guidelines assign different levels of containment for experiments in which DNA from different sources is to be introduced into an *E. coli* K-12 host-vector system. The variation is based on both facts and assumptions. There are some prokaryotes (bacteria) which constantly exchange DNA with *E. coli*. Here it is assumed that experimental conditions beyond those obtained in careful, routine microbiology laboratories are super-



fluos, because an exchange experiments have undoubtedly been performed already in nature.

In every instance of artificial recombination, consideration must be given to the possibility that foreign DNA may be translated into protein (expressed), and also to the possibility that normally repressed genes of the host may be expressed and thus change, undesirably, the characteristics of the cell. It is assumed that the more similar the DNAs of donor and host, the greater the probability of expression of foreign DNA, or of possible derepression of host genes. In those cases where the donor exchanges DNA with *E. coli* in nature, it is unlikely that recombination experiments will create new genetic combinations. When prokaryote donors not known to exchange DNA with *E. coli* in nature are used, however, there is a greater potential for new genetic combinations to be formed and be expressed. Therefore, it is required that experiments involving prokaryotic DNA from a donor that is not known to exchange DNA with *E. coli* in nature be carried out at a higher level of containment. Recombination using prokaryotic DNA from an organism known to be highly pathogenic is prohibited.

There are only limited data available concerning the expression of DNA from higher forms of life (eukaryotes) in *E. coli* (or any other prokaryote). Therefore, the containment prescriptions for experiments inserting eukaryotic DNA into prokaryotes are based on risks having quite uncertain probabilities.

On the assumption that a prokaryote host might translate eukaryotic DNA, it is further presumed that the product of that foreign gene would be most harmful to man if it were an enzyme, hormone, or other protein that was similar (homologous) to proteins already produced by or active in man. An example is a bacterium that could produce insulin. Such a "rogue" bacterium could be of benefit if contained, a nuisance or possibly dangerous if capable of surviving in nature. This is one reason that the higher the phylogenetic order of the eukaryote, the higher the recommended containment, at least until the efficiency of expression of DNA from higher eukaryotes in prokaryotes can be determined.

There is a second, more concrete reason for scaling containment upward as the eukaryote host becomes similar to man. This is the concern that viruses capable of propagating in human tissue, and possibly causing diseases, can contaminate DNA, replicate in prokaryote hosts and infect the experimentalist. Such risks are greatest when total DNA from donor tissue is used in "shotgun" recombinant experiments; it diminishes to much lower levels when pure cloned DNA is used.

The structure of the classification for permissible experiments is based, therefore, on assumptions governing potential risk. It should be emphasized again that although recombinant DNA experiments have now been performed for over five years in hundreds of laboratories throughout the world with hundreds of thousands of different recombinant DNA molecules produced, no case of hazard has been demonstrated.

Part III of the guidelines assigns to each specified class of experiments a

level of physical containment and a level of biological containment at which the experiment shall be performed. As noted before, there is 10,000- to 100,000-fold protection in going from a class I or II biological safety cabinet to a class III biological safety cabinet (i.e., from P3 to P4). Similarly, in going from P1 to P3 there may be a 10,000- to 100,000-fold increase in safety. For biological containment, there is the criterion for HV2 systems that "escape of the recombinant DNA either via survival of the organisms or via transmission of recombinant DNA to other organisms should be less than  $1/10^8$  under specified conditions." However, that criterion is not relative to the HV1 host-vector systems but absolute; thus, this might be a characteristic found for some host-vectors in the HV1 system, but it is mandated for all HV2 systems. This level was chosen. It was pointed out, because it represents a practical limit which one can measure experimentally.

#### Use of *E. coli* K-12

A number of comments were made concerning the use of *E. coli* host-vector systems. It was observed that because *E. coli* K-12 is currently a "poor" pathogen doesn't mean that it might not be converted to a "good" pathogen with the addition of one or two genes; the enfeebled nature of *E. coli* K-12 "is presumably the consequence of mutation(s) introduced during its laboratory passage," but that perhaps different strains of K-12 with different histories may not all be similarly enfeebled.

Further, it was claimed that the failure to convert K-12 to a pathogen by the use of certain plasmids or *Salmonella* genes is not definitive; to be definitive, we must have the detailed nature of the mutations in K-12 "which prevent the expression of pathogenicity." Also, it was noted that there is no way to assess the absolute risk associated with these experiments, and that it is important to assess the potential harm not only to man but to plants, animals, and the environment.

Another commentator urged that this section be supplemented with the evidence from the Falmouth Conference to show that the potential risk is minimal. A commentator cited the potential risk on the basis that "virtually any highly conserved physiologically active eukaryotic protein . . . or fragment thereof could be highly toxic when introduced out of context by a bacterium which received the appropriate gene in a recombination experiment." This criticism of the *E. coli* K-12 system does not detract from the scientific knowledge over the past two years of the great safety of this

system. This evidence is presented in detail in the Environmental Impact Assessment. I agree that different strains of K-12 with different histories may not all be similarly enfeebled and that failure to convert K-12 to a pathogen to date does not prove it can never happen. However, the safety of *E. coli* K-12 has been clearly shown, and there is no need to limit or specify particular strains for EK1. After 30 years of work with many different strains, there is still no known pathogenic *E. coli* K-12 strain. Thus, there is presumptive evidence that all K-12 strains are safe. They are well suited for laboratory experiments because they take up DNA easily, but their cell wall makes them unsuited to compete in nature with wild-type *E. coli*.

On the basis of the Falmouth Conference (which is discussed further in the Environmental Impact Assessment), the conclusion can be drawn that it is essentially impossible for *E. coli* K-12 to be transformed by recombinant DNA into a wild-type, pathogenic *E. coli*. An *E. coli* K-12 containing toxic genes through recombination could theoretically present a risk to a laboratory worker who accidentally ingested it; but it would only be to that laboratory worker. There is evidence to show that harmful genes will have a very low probability of being transferred from *E. coli* to another organism. The plasmids used at the HV2 level are engineered so that they neither self-transfer nor transfer when another plasmid induces conjugation. Thus, the high degree of safety of this system is clear and explains why it is preferable to any other host-vector system at present.

#### General Classification

Disagreement was expressed over whether the PRG-RAC was too stringent or too lax. Those arguing the former position maintain that the guidelines should be relaxed even further because all the experimental evidence gathered and analyzed in the past 2 years indicates that the initial fears concerning the potential hazards were extremely exaggerated; moreover, the benefits to be derived from the research are great. Also, it is pointed out that recombinant DNA experiments not allowed under the current NIH guidelines are proceeding with the approval of responsible national committees in a number of European countries. Those opposing this view argue that there is a lack of experimental data for a sound evaluation of the potential risks, and the fact that a recombinant DNA experiment is permitted in Europe is irrelevant to the establishment of standards in the United States.

#### Recombinant DNA Experiments Involving Viral DNA



Many of the commentators agreed that both the original guidelines and the PRG-RAC were overly stringent with regard to virus experiments. In commenting on the PRG-RAC, the EMBO Standing Committee on Recombinant DNA Research wrote:

The EMBO Committee believes that the containment categorization of experiments with animal virus DNA's which is proposed by the NIH Advisory Committee is too indiscriminate and excessively stringent considering the proposed classification of experiments with other classes of DNA and the longstanding, accepted safety precautions for handling intact virus particles and viral nucleic acids \* \* \*. The EMBO Committee proposes that it would be more reasonable either to consider experiments with viral DNA on a case-by-case basis or to produce a detailed set of recommended categories for experiments with specific viral DNA's. The EMBO Committee hopes in the near future to establish an ad hoc international group of virologists to draw up such proposals.

In response to this suggestion (i.e., for an international group of virologists to consider this issue), a joint U.S.-EMBO Workshop To Assess Risks for Recombinant DNA Experiments Involving the Genomes of Animal, Plant, and Insect Viruses was held in Ascot, England, on January 26-28, 1978. The workshop was attended by 27 distinguished scientists from the United States, the United Kingdom, West Germany, Finland, France, Sweden, and Switzerland. The report of the "Ascot" Workshop was published in the FEDERAL REGISTER on March 31, 1978, and appears as appendix E to the accompanying Environmental Impact Assessment. The workshop concluded:

The probability that K-12 organisms carrying viral DNA inserts could represent a significant hazard to the community was so small as to be of no practical consequence \* \* \* viral genomes or fragments thereof, cloned in *E. coli* K-12 using approved plasmid or phage vectors, pose no more risk than work with the infectious virus or its nucleic acid and in most, if not all cases, clearly present less risk. In fact, the workshop participants agreed that cloning of viral DNA in *E. coli* K-12 may provide a unique opportunity to study with greatly reduced risks the biology of extremely pathogenic and virulent viruses.

On April 6-7, 1978 (as announced on March 17 in the FEDERAL REGISTER), a working group sponsored by the RAC, composed of distinguished American microbiologists, met to review the report of the "Ascot" Workshop. The report of this working group appears as appendix F to the accompanying Environmental Impact Assessment. The working group unanimously endorsed the "Ascot" report with certain minor amendments. Their report included recommended new language to be inserted in the PRG-NIH in place of the sections dealing with viruses in the PRG-RAC. This report was pre-

sented to the RAC at its April 27-28, 1978, meeting, and was unanimously endorsed by the RAC with certain minor amendments. I have accepted these recommendations of the RAC, with certain additional minor amendments, and these now constitute the sections dealing with viruses in part III of the PRG-NIH.

#### *Recombinant DNA Experiments Involving DNA from Plants and Plant Pathogens*

One of the comments made at the December 1977 meeting of the Advisory Committee to the Director, NIH was that "the NIH guidelines do not adequately deal with the use of recombinant DNA in plants \* \* \*". Other commentators have expressed similar sentiments, and the suggestion has been made that "a subcommittee be formed to deal with plants and plant pathogens and make specific recommendations for revision of the guidelines." In response, a Workshop on Risk Assessment of Agricultural Pathogens, composed of distinguished American plant pathologists, was held on March 20-21, 1978 (as announced on March 6 in the FEDERAL REGISTER). Sponsored by the U.S. Department of Agriculture, the National Science Foundation, and the NIH, the report of this workshop appears as appendix G to the accompanying Environmental Impact Assessment. The report was presented to the RAC at its April 27-28, 1978, meeting and was unanimously endorsed by the RAC with certain minor amendments. I have accepted these recommendations of the RAC with certain additional minor amendments; these involve changes in the PRG-NIH in sections dealing with the use of plants and plant pathogens in recombinant DNA research.

Using the 10 criteria previously discussed in light of what is known today, I believe the revisions in containment standards proposed by the PRG-NIH are sound. The changes in containment standards in the PRG-NIH are discussed below in greater detail for each of the subsections of part III.

#### SPECIFIC CONSIDERATIONS

##### *Section III—Opening Paragraphs*

As discussed above in part I of this document, the section of the guidelines numbered III-A in both the 1976 guidelines and the PRG-RAC and entitled "Experiments That Are Not To Be Performed" has been moved in the PRG-NIH to become section I-D entitled "Prohibitions." This leads to a renumbering of the remaining subsections of part III of the PRG-NIH as compared to the PRG-RAC.

Two new paragraphs have been inserted at the beginning of part III of the PRG-NIH. The first reminds the reader to consult part I "where listings

are given of prohibited and exempt experiments."

The second inserted paragraph is a "general flexibility clause." Insertion of such a "clause" was recommended by the RAC at its April 27-28, 1978, meeting. It recognizes that the classification of experiments given in part III will necessarily be imperfect, as investigators in the future devise new ways to conduct recombinant DNA experiments not currently foreseen and therefore not explicitly considered in the guidelines. Also, new data may become available showing that certain particular experiments currently assigned a particular containment level are, indeed, clearly more (or less) safe than envisioned at this time. Therefore, this "clause" states that "changes in these levels for specific experiments (or the assignment of levels to experiments not explicitly considered here) may be expressly approved by the Director, NIH, on the recommendation of the Recombinant DNA Advisory Committee (RAC)."

##### *Section III-A-1-a. Shotgun Experiments into *E. coli* K-12 with Inserted Eukaryotic DNA*

At a number of places in this subsection the principal investigator is allowed to choose between two combinations of containment procedures. For example, in several instances one is permitted to use P2+EK1 or P1+EK2. This was endorsed by some commentators but questioned by others. This concept of flexibility was addressed in part II of this document. I also wish to point out that the concept is not a new one—it was allowed under the original guidelines. Based upon events of the past 2 years, the RAC merely proposed that this principle be extended to certain specified additional cases where they believe it appropriate. I agree with their proposals and have therefore included in the PRG-NIH all such specific cases of flexibility recommended in the PRG-RAC.

On the other hand, in certain other specific cases (e.g., DNA from birds) the PRG-RAC recommended the containment level be P2+EK2, without the option of P3+EK1. Certain commentators urged that in all cases where the containment level of P2+EK2 is given, the option of P3+EK1 be allowed. However, the RAC felt that in view of their increased confidence in the biological containment offered by the EK2 system, P2+EK2 offers more containment than P3+EK1, and that P2+EK2 without the option of P3+EK1 should be the containment level for certain specified classes of experiments. I accept the view of the RAC and have therefore specified in the PRG-NIH the containment levels of P2+EK2 without the option of



P3+EK1 in every case where it appeared in the PRG-RAC.

The section of this document on "Recombinant DNA Experiments Involving Viral DNA" discussed the "Ascot" workshop report, and the April 6-7, 1978, working group report which endorsed the "Ascot" report. The RAC at its April 27-28, 1978, meeting unanimously endorsed the working group report recommending lower containment levels for deliberate cloning of viral DNA into *E. coli* K-12 (see below for discussion of section III-A-2). One of the reasons given originally for the higher containment level for shotgun experiments involving primate DNA into *E. coli* K-12 was the possible inadvertent cloning of viral DNA. In view of their recommendation of lower containment for deliberate cloning of viral DNA into *E. coli* K-12, the RAC on April 27-28, 1978, reconsidered primate shotgun levels, and voted unanimously for new language as follows: "Primates. P2 physical containment + an EK2 host-vector. Any lowering of containment below these levels (i.e., for purified DNA or characterized clones) cannot be made solely by an institutional biosafety committee but requires NIH approval." I have accepted this new language and inserted it in the PRG-NIH, as well as a similar lowering of containment for shotgun cloning of cold-blooded vertebrate DNA into *E. coli* K-12.

One commentator noted that section III-B-1-a-(1)-(g) of the PRG-RAC entitled "Cloning of Viral Genomes From Eukaryotic Cell DNA" . . . "focuses on cloning integrated retrovirus nucleotide sequences from mammalian cell DNA but says nothing about nucleotide sequences of integrated DNA viruses." This entire section has been eliminated from the PRG-NIH and instead a new subsection III-A-2-a-(3) entitled "Intracellular Viral DNA" has been added to the PRG-NIH which covers both integrated retroviruses and DNA virus sequences; it says, "Physical and biological contaminant specified for shotgun experiments with eukaryotic cellular DNA (See section III-A-1a) shall be used for DNA recombinants produced with integrated viral DNA or viral genomes present in infected cells."

#### Section III-A-1-b. Shotgun Experiments Into *E. coli* K-12 With Inserted Prokaryotic DNA

In the 1976 guidelines, the section (III-B-2-a)-(ii) dealing with shotgun experiments into *E. coli* K-12 with inserted prokaryotic DNA was subdivided into two sections, i.e., "Prokaryotes That Exchange Genetic Information With *E. coli*" and "Prokaryotes That Do Not Exchange Genetic Information With *E. coli*." In the

PRG-RAC it was assumed that all prokaryotes that exchange genetic information with *E. coli* would be exempt from the guidelines by appearing on the "list of nonnovel exchangers." Therefore, in the PRG-RAC the section (III-B-1-a-(2)) dealing with shotgun experiments into *E. coli* K-12 with inserted prokaryotic DNA actually considered only prokaryotes that did not exchange genetic information with *E. coli*. The problem with this approach was discussed by commentators, focusing especially on the case of *Agrobacterium tumefaciens*. It meant that a prokaryote which exchanges genetic information with *E. coli*, and was therefore properly assigned a low containment level under the 1976 Guidelines, would under the PRG RAC either appear on the "list" and therefore be exempt from the guidelines, or if for some reason it did not appear on the list, the containment level would actually in some cases be raised. This was not the intent of the RAC. Therefore, I proposed to the RAC, and they accepted at their April 27-28, 1978, meeting, that language be reinserted in the the PRG-NIH covering prokaryotes that exchange genetic information with *E. coli* but which do not appear on the list. This section in the PRG-NIH (III-A-1-b-(1)) reads:

*Prokaryotes That Exchange Genetic Information [35] with E. coli.* It is expected that many of the prokaryotes that exchange genetic information with *E. coli* by known physiological processes will be exempted from these guidelines by appearing on the "list of exchangers" (see sec. I-E-4).

For those not on the list, the containment levels are P1 physical containment + an EK1 host-vector. In fact, experiments in this category can be performed with *E. coli* K-12 vectors exhibiting a lesser containment (e.g., conjugative plasmids) than EK1 vectors. However, for prokaryotes that are classified [1] as Class 2 the containment levels are P2+EK1.

For prokaryotes that do not exchange genetic information with *E. coli*, the PRG-RAC proposed that P1+EK2 or P2+EK1 conditions apply only in cases of extensive characterization and RAC approval. "Experiments with DNA's from bacteria that are not extensively characterized require P2 physical containment + an EK2 host-vector or P3+EK1. Experiments with DNA's from pathogenic species (class 2 and plant pathogens, see App. B) must use P3+EK2." A number of commentators objected to two different aspects of this subsection of the PRG-RAC: (1) Many felt that experiments involving nonpathogenic prokaryotes should be conducted at P1+EK2 or P2+EK1 without extensive characterization or RAC approval; (2) It was argued that plant pathogens should not be included with CDC class 2 agents as requiring P3+EK2 containment. Both of these comments were referred to the RAC at their April 27-

28, 1978, meeting and they agreed with the commentators. Therefore, this Section of the PRG-NIH (III-A-1-b-(2)) reads:

(2) *Prokaryotes that Do Not Exchange Genetic Information with E. coli.* P2 physical containment + an EK1 host-vector, or P1+EK2, except for DNA from class 2 agents, [1] which require P3+EK2.

The EMBO Standing Advisory Committee on Recombinant DNA Research recommends that the containment level for all novel non pathogenic prokaryotic DNA into *E. coli* K-12 be P1+EK1. It is my opinion that it is prudent to retain the levels of P2+EK1 or P1+EK2 for nonpathogenic prokaryotes that do not exchange genetic information with *E. coli*.

The PRG-RAC received substantial criticisms for identifying all agents classified as class 2 in the CDC's publication "Classification of Etiologic Agents on the Basis of Hazard" (Fourth edition, July 1974) as being pathogenic for the purpose of assigning containment levels. Many commentators stated that many of the organisms so classified were harmless and others were of such low pathogenicity that severe safety precautions were unwarranted. It was also pointed out that the pathogenicity of an intact micro-organism and the conjectural hazard of a piece of DNA from such an organism within *E. coli* K-12 were quite different matters. It should be noted that the difficulties in application of the CDC classification for the purposes of these guidelines was recognized in the original guidelines. For example, all species of *Salmonella* are classified as class 2 organisms by CDC. The original guidelines, however, distinguish between the pathogenicity of *S. typhimurium* and *S. typhi* for the assignment of containment levels. I have therefore accepted the suggestion of these commentators and have added footnote 1 to the PRG-NIH. This gives NIH the authority, upon the recommendation of the RAC, to designate certain agents which are listed as class 2 by CDC as class 1 agents for the purpose of these guidelines.

#### Section III-A-2-a. DNA from viruses of eukaryotes into *E. coli* K-12

Discussed earlier within part III of this document under the heading "Recombinant DNA Experiments Involving Viral DNA" was the history of the "Ascot" workshop report (App. E to the accompanying environmental impact assessment) and the report of the working group which met on April 6-7 1978 (App. F to the accompanying environmental impact assessment). Section III-A-2 of the PRG-NIH adopts the recommendations of the working group with minor modifica-



tion. It is based on a reassessment made by these experts in the field of virology of the potential hazards of inserting pieces of viral DNA into *E. coli*. I believe the argument presented in the "Ascot" report and the working group report are well founded, specifically that "the probability that K-12 organisms carrying viral DNA inserts could represent a significant hazard to the community was so small as to be of no practical consequence . . . viral genomes or fragments thereof, cloned in *E. coli* K-12 using approved plasmid or phage vectors pose no more risk than work with the infectious virus or its nucleic acid and in most, if not all, cases clearly present less risk." Accordingly, section III-A-2-a of the PRG-NIH has been completely rewritten.

**Section III-A-2-b. Eukaryotic Organellar DNA into *E. coli* K-12**

To be consistent with the one step lowering of physical containment described earlier for shotgun experiments with primate DNA, the levels for mitochondrial DNA from primates has been similarly lowered by one step in physical containment in the PRG-NIH as compared to the PRG-RAC.

**Section III-A-3. Lowering of containment for characterized or purified DNA preparations and clones**

Concern was expressed by several commentators regarding the revisions in the PRG-RAC which would allow the local IBC (with notification to be sent to NIH) to reduce either the biological or physical containment level by one step if (1) the DNA is 99-percent purified and shown to be free of harmful genes prior to its insertion into a recombinant molecule, or (2) if subsequent to insertion the clone is rigorously characterized and shown to be free of harmful genes. In the original guidelines lowering in case (2) could only be done with NIH prior approval.

There was support from several commentators for the changes in this subsection. The rationale is explained in new language inserted into this section of the PRG-RAC, which is retained in the PRG-NIH; i.e.:

Many of the risks which might conceivably arise from some types of recombinant DNA experiments, particularly shotgun experiments, would result from the inadvertent cloning of a harmful sequence. Therefore, in cases where the risk or inadvertently cloning the 'wrong' DNA is reduced by prior enrichment for the desired piece, or in which a clone, made from a random assortment of DNAs, has been purified and the absence of harmful sequences established, the containment conditions for further work may be reduced.

Some commentators noted the ambiguity and difficulty attendant in the phrase "free of harmful genes." The EMBO Standing Advisory Committee

on Recombinant DNA Research reports that "several national guidelines for recombinant DNA research state that containment measures may be relaxed once a cloned DNA fragment has been biochemically characterized and shown to be free of harmful genes (NIH guidelines) or devoid of any known pathogenic characteristic (French guidelines). The EMBO committee believes the latter to be a more feasible requirement, but neither can readily be met, and the committee finds it difficult to suggest what sorts of experimental tests might be devised to meet these requirements."

I agree that "the terms 'characterized' and 'free of harmful genes' are unavoidably vague." However, footnote 3 of the PRG-NIH goes on to list five types of data which should be considered in making this determination.

Some commentators were also concerned that this grant of additional authority to the local IBC's for single step lowering in containment levels might introduce variability in the application of the guidelines. I have considered this possibility and have decided that the principle of promoting local involvement in the implementation of the guidelines outweighs the difficulties which may be encountered in this process. In an attempt to minimize these problems, I have (1) attempted to make all parts of the guidelines as clear, specific, and unambiguous as possible, and (2) expanded the "Roles and Responsibilities" section to outline functions and responsibilities in greater detail. Also, the guidelines require that the Office of Recombinant DNA Activities at the NIH be notified in writing of such an action. A mechanism is therefore in place to ensure that such actions proceed with an acceptable degree of uniformity.

The question was raised whether a clone, the containment level of which was lowered by the IBC at Institution X, may after shipment to Institution Y still be used at the lower level without review by the IBC at Institution Y. It clearly has been, and remains, the intention of both the RAC and myself that the IBC at the receiving institution must approve the reduction in containment for the handling of the clone in such a situation. The investigator at the receiving institution must handle the clone at the higher level until such permission is granted.

One commentator urged that prior cloning be accepted as a technique for the purification of DNA molecules prior to their reinsertion in a new recombinant DNA molecule. The PRG-RAC specified that purification must be achieved "by physical or chemical techniques." The criterion for the single step reduction in containment levels in this situation is that the DNA

preparation be 99 percent pure; I see no reason to so restrict the means by which such purification is attained. I have accepted this suggestion as a means of better serving the needs of the investigator without reducing the margin of safety to the public and the environment, and therefore have stricken from the PRG-NIH the words "by physical and chemical techniques" following the word "purified."

One commentator noted that the PRG-NIH might be interpreted as allowing a single step reduction in containment levels for purification of the DNA prior to its insertion into a recombinant DNA molecule, and then a subsequent further single step reduction in containment level once the same molecule was cloned. This was not intended. Therefore, clarifying language has been added in the PRG-NIH stating that an IBC "may give approval for a single step reduction in physical or biological containment on receipt of evidence of characterization of a clone derived from a shotgun experiment and its . . ."

Finally, as noted above in this document under "Section III-A1-a—Shotgun Experiments into *E. coli* K-12 With Inserted Eukaryotic DNA," the RAC recommended at its April 27-28, 1978, meeting (and I have accepted the recommendation and inserted it in the PRG-NIH), that the containment levels for shotgun of primate DNA into *E. coli* K-12 be lowered to P2+EK2. However, on the recommendation of the RAC, a stipulation added in section III-A-1-a of the PRG-NIH is that for primate shotgun "any lowering of containment below these levels (i.e., for purified DNA or characterized clones) cannot be made solely by an institutional biosafety committee but requires NIH approval." Language stating this limitation in authority of the IBC with regard to primate DNA has been inserted into subsection III-A-3 of the PRG-NIH, as has language indicating that any lowering of containment under this section to levels below P1+EK1 requires prior NIH approval.

**Section III-B. Experiments with Other Prokaryotic Host-Vectors**

Some commentators felt that the PRG-RAC unnecessarily emphasized the use of *E. coli* K-12 and would not allow important recombinant DNA experiments to be done in other prokaryotic hosts. Section III-B describes the use of prokaryotic host-vector systems other than *E. coli* K-12 which have been approved as HVI hosts. It should be remembered that "self-cloning experiments with prokaryotic hosts are exempt from the guidelines under exemptions I-E-2 and I-E-3 and that other experiments involving DNA segments from species that exchange



DNA by known physiological processes are exempt from the Guidelines under exemption I-E-4.

The RAC at its April 27-28, 1978, meeting pointed out that there are certain scientifically important experiments which are very safe but which neither fit the criteria to be exempt from the guidelines, nor the criteria for HVI certification. A new section III-B-2 has been added to the PRG-NIH to cover these cases and assign appropriate containment levels. In these experiments DNA from a prokaryotic host (Host X) is cloned into *E. coli* K-12 (this situation is already covered in sec. III-A-1-b(2) of the guidelines); in the second part of the experiment the recombinant DNA (consisting of DNA sequences from Host X linked to an *E. coli* plasmid or bacteriophage) is returned to Host X and propagated there.

#### *Section III-C. Experiments with eukaryotic host-vectors*

A number of commentators felt that the stringent containment conditions required both in the original guidelines and in the PRG-RAC for introduction of recombinant DNA into tissue culture cells, using viruses as vectors, were unwarranted. The EMBO Standing Advisory Committee on Recombinant DNA Research wrote:

In experiments involving the introduction of foreign DNA into cultured cells of animals using DNA viruses as vectors, biological containment is assured by the very restricted permissive conditions for the host cells: the only routes by which the recombinant molecule might escape are by chance infection of a contaminating microorganism or within a viral capsid and the size of the recombinant molecule may well preclude its encapsidation \* \* \*. For example, cloning of mouse DNA using polyoma virus as a vector and mouse cells as host should not require precautions more stringent than those routinely used for many years in laboratories studying polyoma virus infection of mouse cells and mice. The EMBO Committee finds the proposals for this class of experiments in the revised NIH Guidelines not sufficiently discriminating because they would impose unnecessarily high levels of physical containment for experiments with many eukaryotic DNA's.

Discussed earlier within Part III of this document under the heading "Recombinant DNA Experiments Involving Viral DNA" was the history of the "Ascot" workshop report (See App. E to the accompanying environmental impact assessment, and the report of the working group which met on April 6-7, 1978 (App. F to the accompanying environmental impact assessment). I have accepted the recommendations of the work group and incorporated their suggested revision of this section which now becomes section III-C of the PRG-NIH. The result of this change is that section III-B-3 of the PRG-RAC "Experiments with Eukar-

yotic Host-Vectors," subparts (a) "Vertebrate Host-Vector Systems," and (b) "Invertebrate Host-Vector Systems," are eliminated; substituted for it in the PRG-NIH is new language derived from the working group report which become section III-C "Experiments With Eukaryotic Host-Vectors," subparts (1) Vertebrate Host-Vector System"; (2) "Invertebrate Host-Vector Systems in which Insect Viruses Are Used To Propagate Other DNA Segments", and (3) "Plant Viral Host-Vector Systems."

#### *Section III-C-4. Plant Host-Vector Systems Other Than Viruses*

Discussed earlier within Part III of this document under the heading "Recombinant DNA Experiments Involving DNA From Plants and Plant Pathogens" was the Workshop on Risk Assessment of Agricultural Pathogens, held on March 20-21, 1978, sponsored by USDA, NSF, and NIH. Based on the Workshop report (See Appendix G to the accompanying Environmental Impact Assessment), section III-D of the PRG-NIH has been rewritten.

#### *Section III-C-5. Fungal or Similar Lower Eukaryotic Host-Vector Systems*

Both the 1976 Guidelines and the PRG-RAC used the same short paragraph for this section, giving little detail, because they noted "the development of these host-vector is presently in the speculative stage." Since that time a specific host-vector system of this class has been developed, i.e., *Saccharomyces cerevisiae* (baker's yeast), and other similar systems may also soon be proposed. Accordingly, this section (III-C-5) of the PRG-NIH has been expanded to give more specific instructions on appropriate containment levels.

#### *Section III-D. Complementary DNAs*

Since specific containment levels for the use of purified cDNA of viral mRNA are now given in section III-A-2-a of the PRG-NIH, a sentence has been added noting this at the beginning of section III-D of the PRG-NIH. Otherwise, the rest of this evoked no comments and remains identical in the PRG-NIH to the PRG-RAC.

#### *Section III-E. Synthetic DNA*

Because synthetic DNA is now explicitly included in the PRG-NIH (as discussed in section I of this document), it was necessary to add language to Part III of the PRG-NIH detailing the appropriate containment levels for these experiments. The RAC at its meeting on April 27-28, 1978, approved such language, and it has been inserted in the PRG-NIH as section III-E.

## IV. ROLES AND RESPONSIBILITIES

### REVIEW OF RAC PROPOSED GUIDELINES

This section, as in the 1976 Guidelines, provides an administrative framework for implementation. Modifications to the various roles and responsibilities proposed by the RAC are listed below.

#### *Institutional Responsibilities*

**Institution.** Several changes were proposed in the PRG-RAC as compared to the 1976 Guidelines in the responsibilities of the institution. Responsibilities that were added or further detailed included: (1) a requirement for insuring the training of research personnel and the use of good microbiological technique, and (2) a requirement to determine the need for medical procedures, with recommendations of possible specific practices.

**Institutional Biosafety Committees.** Membership of the committees was clarified by a recommendation to include other than scientific members. In the PRG-RAC (section III), institutional biosafety committees (IBCs) are given the discretion to approve single-step reductions in containment levels for experiments with characterized clones and purified DNA. The IBC's would be required to notify the NIH Office of Recombinant DNA Activities (ORDA) of these approvals.

**Biological Safety Officer.** Institutions at which P3 and P4 level recombinant DNA work is conducted would be required to have a biological safety officer, whose specific roles and responsibilities are outlined.

**Principal Investigator.** The role and responsibilities of the principal investigator would remain basically the same except for the important addition of a requirement for training in microbiological techniques. Responsibility for the determination of the practices necessary for medical surveillance would be relocated to the institution.

#### *NIH Responsibilities*

**Office of the Director.** The responsibilities of the Director would remain unchanged. A sentence was added which clarified the Director's authority to implement the Guidelines and to be the final arbiter in the interpretation of the Guidelines.

**Recombinant Advisory Committee.** There were no changes in the current responsibilities of the RAC; however, there were clarifications of the scope of some duties, for example, the certification process. The language of the 1976 Guidelines caused confusion among some concerning the certification of EK2 (HV2) and EK3 (HV3) host-vector systems. In practice, the certification process involved a two-step procedure: (1) the RAC's recommendation to the Director, NIH, that



a particular host-vector system be certified; and (2) certification of the system by the Director, NIH. The PRG-RAC clarifies the fact that a two-step procedure is followed. The rationale for the two-step procedure is that it allows the Director, NIH, to solicit the opinions of additional experts prior to making a final decision on certification.

The RAC's authority to recommend exceptions from the prohibitions was also clarified. The 1976 version of the Guidelines envisioned the possibility of the RAC's recommending an exception to the 10-liter limit on culture volume for recombinant DNA's known to make harmful products. The proposed revision would extend the possibility of an exception to the five other classes of currently prohibited experiments. The general rationale for this addition is the RAC's inability to foresee all possible future circumstances and the RAC's desire to specify, within the limits of strict safeguards, the possibility of an exception for compelling social or scientific reasons. A more immediate and specific justification for the paragraph on exceptions from the prohibitions is that the risk-assessment studies necessary for a clearer understanding of the potential biohazards of recombinant DNA research may not be able to be carried out without technical violations of the current Guidelines, unless there is a mechanism for approving exceptions.

#### REVIEW OF COMMENTS AND NIH PROPOSED GUIDELINES

As in the public hearing on the originally proposed Guidelines in 1976, many public commentators urged openness, candor, and public participation in the revision process, emphasizing shared responsibility and accountability from the local to the national level. We have heeded these suggestions. In addition to holding all RAC meetings in the open and holding a public hearing on the PRG-RAC in December 1977, we have published both the PRG-RAC and now the PRG-NIH in the *FEDERAL REGISTER* for public comment.

It remains clear, as stated in my 1976 decision, that much of the success of the guidelines will depend on the wisdom with which they are implemented. The recommendations of the PRG-RAC have been carefully weighed along with other public and scientific comments received on the "roles and responsibilities" section. In general, I have adopted the RAC proposals with certain additional modifications based on issues raised by the Director's Advisory Committee and other commentators. The issues I have considered, and a discussion of them follows:

#### *Responsibilities of the institution (general)*

Again, as in 1976, this section of the guidelines drew considerable comment directed to the roles and responsibilities of the institution and its several constituents. Generally, commentators requested more information and greater clarification of the structure and operation of the IBC, the function of the biological safety officer, and the duties of the institution. Because of the importance of this section with regard to successful implementation of the guidelines, and therefore safe conduct of this research, these suggestions and comments have been carefully considered. NIH acknowledges its special responsibility in assuming leadership in developing and promoting safety programs relevant to recombinant DNA research. Therefore, as in 1976, another committee chaired by Dr. W. Emmett Barkley, Director, Office of Research Safety, NCI, was convened to address concerns raised. As a result, and in response to a number of commentators' requests, appendix D of the original guidelines has been restored and enhanced to give additional advice on safety matters (see "Laboratory Safety Monograph—A Supplement to the NIH Guidelines for Recombinant DNA Research"). The revised guidelines also retain requirements for emergency plans to cover accidents as well as strengthening the requirement for training of all recombinant DNA researchers in safe laboratory procedures.

The intent of this section, as before, is to integrate safety practice into the conduct of recombinant DNA research and to assign responsibilities for this to the principal investigator institution, IBC, and biological safety officer. Therefore, it is important that these responsibilities be stated in an unambiguous manner. For this reason, and in response to many commentators, Part IV has been restructured, to distinguish in greater detail and more clearly align some of these functions. The appendices contain additional complementary information on roles and responsibilities, including information for IBC's and biological safety officers.

In response to several comments, the scope of review of research has been broadened to cover all recombinant DNA research at an institution receiving funds from NIH for recombinant DNA research, whether or not the specific recombinant DNA project is being funded by NIH. While this increases the responsibility of the institution and the IBC's, it is believed that this revision will enhance the overall safety of the conduct of this research. Furthermore, at the suggestion of one commentator, I have decided to

change the name of the biohazards committees to biosafety committees to reflect the spirit of the guidelines more closely.

Several generic comments deserve to be highlighted as they represent significantly increased authority to be delegated to the institution. In 1976, the RAC did not accept commentators' suggestions for requiring local committees to make an independent evaluation of the containment levels required by the guidelines for individual research projects. I therefore stated in the 1976 decision that NIH would not require local institutions to have their committees perform this function, although they would not be prohibited from doing so. Commentators have now noted that in order for an IBC to accomplish its mandated responsibilities under the 1976 guidelines, including reviewing and approving recombinant DNA research projects, it has been necessary for the committee implicitly to determine containment conditions. Therefore, in order to better clarify its role, the assessment of appropriate containment levels is now made an explicit responsibility of the IBC.

In addition, institutions through their IBC's will be given increased responsibility for primary oversight of this research as they have now been delegated the authority from NIH to approve or disapprove proposed recombinant DNA projects. NIH through ORDA will conduct a review of institutional actions, upon registration of the projects, to ensure compliance with the NIH guidelines, thereby maintaining a national standard for the research. This action has been in response to several comments calling for increased local responsibility and a more simplified administrative process with regard to gaining approval for this research to proceed. In view of the impossibility of Federal surveillance to enforce these standards externally, I feel it is essential to increase the authority and responsibility of the local institution. It was also requested that IBC's have a role if legislation in this area is adopted, and this concept is endorsed in the bill report of March 24, 1978, on the Recombinant DNA Act, by the House Committee on Interstate and Foreign Commerce, which says, "It is the view of the committee that the appropriate portions of the administrative requirements of section IV of the NIH guidelines are a reasonable model upon which the Secretary could base administrative regulations. In particular, the current practice in the NIH guidelines of delegating to local biohazards committees most of the responsibility for the inspection of facilities and the approval of the specific safety requirements appropriate to each project or activity is an effective



tive and relatively inexpensive administrative mechanism."

As in the 1976 decision, a number of recommendations were received regarding the membership of IBC's. In 1976, suggestions were made for broadening IBC representation to include members not only from various disciplines related to recombinant DNA molecule technology, biological safety, and engineering but also to include those knowledgeable in applicable laws, regulations, standards of practice, community attitudes, and health and environmental considerations. Consequently, at that time I recommended in my decision that these diverse points of view be included or made available to the committees. The language in the PRG-RAC requires a diversity of membership, but does not mandate noninstitutional members. In response to several requests, and in view of increased responsibility at the local level, I am now going beyond the RAC proposal and adding a provision that "no IBC may consist entirely of persons who are officers, employees, or agents of, or are otherwise associated with the institution, apart from their membership on the IBC." Other specific categories for membership are not mandated although the PRG-NIH now states that "membership should include individuals from disciplines relevant to recombinant DNA technology, biological safety, and engineering"; that it is recommended that "at least one member be a nondoctoral individual from a laboratory technical staff"; and that the IBC "include members knowledgeable about such matters as applicable law, standards of professional conduct and practice, community attitudes, and the environment."

The possibility of conflict between IBC's and local community oversight committees was raised. With noninstitutional membership on IBC's I believe there is no need to have additional community committees.

A number of other recommendations were received from public commentators relating to more specific issues; they are considered below under the appropriate headings.

#### *Responsibilities of the institution (specific)*

**Institution.** A number of points were raised by commentators concerning health monitoring by institutions. NIH was requested to develop a model for institutional medical surveillance for recombinant DNA research workers. The issue of medical monitoring is one of considerable interest to the NIH. This is a general problem not unique to recombinant DNA research. As one commentator noted, instituting a routine health monitoring and reporting program for personnel en-

gaged in areas of research besides recombinant DNA, such as tumor viruses and pathogenic organisms, is important. However, the state-of-the-art is primitive in terms of what can be done to monitor workers' health generally, but particularly in the area of recombinant DNA research where there is no known hazard. At my request, an NIH committee reviewed this area and has made recommendations as to what such a program may include. This recommendation, which calls for monitoring illnesses, collecting serum samples, and keeping a register of agents handled, is responsive to several suggestions received on this issue, and it has, therefore, been adopted in the PRG-NIH. Additionally, appendix D will include more detailed information on medical surveillance.

Grievance procedures for workers under the guidelines were requested but this is not considered necessary as the Occupational Safety and Health Act (OSHA) rules and regulations already provide such a mechanism. In the 1976 decision it was also noted that OSHA standards and procedures apply to most institutions, so it was not considered necessary then, or now, to require in the guidelines that IBC's insure OSHA compliance. Further, the Federal Interagency Committee on Recombinant DNA Research, which I chair, includes representatives from the Occupational Safety and Health Administration (Department of Labor), assuring cooperation at the Federal level.

One commentator spoke to the need for a biosafety control manager which would be similar to the head of a campus environmental health and safety office. While such a program and manager may be desirable, it is felt that this is an institutional administrative matter and should not be addressed in the guidelines.

**Institutional Biosafety Committee (IBC).** Several commentators requested more detail on IBC duties and this has been accomplished in the supplement to the PRG-NIH entitled, "Laboratory Safety Monograph." For example, information is included here on facility certification, periodic inspections and monitoring, and a model for IBC operation.

There was concern about the establishment of area biosafety committees and possible jurisdictional disputes between them and institutional biosafety committees. This has been further clarified in the definitions in Part I.

It was suggested that biosafety committee meetings be open to the public. The guidelines currently require only that the minutes be available to the public. In view of possible discussion of proprietary and patentable information, IBC meetings cannot always be open. I do urge, however, that local

committees, when possible, have open meetings and suggest that all meetings be announced.

The question was raised concerning possible conflict of interest of local committee members. This is an important point, and I have added a provision prohibiting an individual engaged in, or expecting to be engaged in, or having a direct financial interest in, a recombinant DNA project from being involved in the review or approval of that project.

Concern was expressed about the cost of IBC operations, and suggestions were made that the Government underwrite this expense. Because NIH already pays, through indirect costs, the operations of such committees, I have decided that there is no need at this time to separate them out from other indirect costs of the institutions.

**Biological Safety Officer.** Because increased authority and responsibility have been given the IBC's, it is appropriate that institutions conducting P3 or P4 level research have someone designated to handle biological safety questions generally.

I have accepted the suggestion that the biological safety officer shall be a member of the IBC because his or her responsibilities are so closely allied to the function of the committee.

Another commentator noted that too much emphasis was placed in the PRG-RAC on the regulatory role of the biosafety officer rather than on his or her role as a technical consultant; therefore, language indicating this latter role has been inserted in the PRG-NIH.

In response to questions on the qualifications of biological safety officers, I note that the officer need not be an M.D. Further, it is not necessary that he or she be engaged in research. Since the passage of the Occupational Safety and Health Act, most institutions have established occupational safety and health departments or programs with institutional safety officers. There are no standard certification procedures for such individuals, although their qualifications, in many cases, could be commensurate with those of a biological safety officer. The supplement to the PRG-NIH entitled, "Laboratory Safety Monograph," provides in greater detail the kinds of qualifications that biosafety officers should have. NIH is developing a training course for campus safety officers, including biological safety officers, and requests for information should be directed to Dr. Emmett Barkley, Director, Office of Research Safety, National Cancer Institute, Bethesda, Md. 20014.

**Principal Investigator.** In response to several commentators, the steps the investigator needs to take in order to have proposed research approved at



the local and national levels have been delineated in Appendix C to the guidelines which contains documentation of NIH administrative procedures for recombinant DNA research projects.

Considerable attention has been given to the issue of training. Several commentators urged that training standards be set by the NIH, preferably in the guidelines. Other commentators wanted the guidelines to direct the institution or IBC to set standards for training; however, some opposed this view. Still others wanted investigator competency evaluated or certified after training had been undertaken. It should be noted that the PRG-RAC represented a strengthening of training requirements, compared to those in the 1976 guidelines. Commentators remain concerned regarding the quality and uniformity of such training. The NIH is responding to this by placing as a high priority the development of training standards and courses. Currently, NIH is supporting a Working Panel of the American Society for Microbiology (ASM) which is considering standards of training in microbiological techniques for recombinant DNA research. When a report is submitted to NIH, it will be shared with institutions, IBC's, and principal investigators for their use. At this time, however, national certification should not be attempted until the ASM/NIH criteria for training have been formulated and subsequently evaluated. It should be noted that, aside from Nuclear Regulatory Commission standards for training for radioisotope work, there are apparently no other formal training criteria presently required for biomedical research. Thus, the work of the ASM Panel will be establishing a precedent. It is for these reasons that I feel NIH should proceed carefully and in stages, at the same time promoting safety training for researchers. Accordingly, NIH will develop courses based on these standards of training and make them widely available.

#### *Responsibilities of the NIH (General)*

**Due Process Considerations.** A focus of public comment at the December hearing was on "procedural due process," to insure public participation in the development of NIH recombinant DNA policies. Much of the public testimony and comment in letters thereafter focused on public representation on committees. Also stressed was the need for public notice of all meetings, and for procedures to insure public participation in the exercise of responsibilities by the RAC, the Office of the Director, NIH, and the Advisory Committee to the Director, NIH.

Several commentators specifically urged that the guidelines spell out the

procedures to be used for the following:

- To develop and amend the list of "non-novel experiments";

- To permit the Director, on the advice of the RAC, to grant exceptions from prohibited experiments, such as for risk-assessment experiments;

- To certify host-vector systems;

- To modify guidelines in the future.

There were also suggestions that guidance be given on how to deal with infractions of the guidelines. Specifically, one commentator suggested that procedures outline in detail:

- How charges of non-compliance could be brought;

- How charges of non-compliance would be evaluated;

- What opportunities would be provided for the principal investigator and his institution to defend themselves against charges; and

- What appeals procedures would be available before the termination of funding or the invoking of other penalties.

Because of the key role of the RAC in the development and monitoring on NIH recombinant DNA policies, a number of comments were directed to its composition and functions. Many commentators focused on the RAC's membership, urging that the guidelines define procedures for nomination and selection of members. Suggestions for potential membership on the RAC included more representation for certain scientific disciplines, such as virology and microbiology; greater representation of individuals skilled in occupational and environmental health and safety; and more public representation, including perhaps a "dissenter" from current NIH policies.

A number of comments concerned Committee operations. The RAC was urged to formalize schedules so that all would know when it would meet over the next 2 to 3 years. Further, it was urged that notices and complete agendas be placed in the *FEDERAL REGISTER* for each meeting; that all documents for Committee consideration be made available to the public; and that the NIH pay for public witnesses to attend meetings of the RAC.

In response to these comments, Part IV of the guidelines has been reorganized extensively. The responsibilities from the local to national level have been stated and defined more clearly. Further, for NIH responsibilities, procedures suggested by commentators have been specified to afford opportunity for public comment. A special appendix to the guidelines includes relevant implementation documents from ORDA that explain the administration of the NIH guidelines at the local and national levels.

From the beginning, the NIH has gone to great lengths to insure proce-

dural due process for the public and scientific communities. The RAC conducts all meetings in the open, and files notice of each meeting in the *FEDERAL REGISTER*. All the documents listed on the agenda of the RAC meetings have been available to the public. Additionally, the Advisory Committee to the Director, NIH, has provided a public forum on the 1976 guidelines and now on the proposed revisions. The public hearing in February 1976 on the originally proposed guidelines resulted in extensive revision of that proposal. The PRG-RAC was published in the *FEDERAL REGISTER* on September 27, 1977, for public comment, and the meeting of the Director's Advisory Committee held in December 1977 was announced in the *FEDERAL REGISTER*. In addition to a general invitation for public testimony, the NIH provided funds for witnesses from the public, private, and scientific sectors to attend and present their views.

The proposed reorganization of Part IV has more clearly defined a structure for responsibilities at the local and national level, with opportunity for public and scientific participation. It makes more formal a process that has been occurring informally. Flexibility, however, remains essential to avoid unnecessary and protracted delays in decisionmaking. Clearly a full panoply of review, including a public hearing, is not essential for most of the functions under the guidelines. For many functions, the need for public review can be met through publication in the *FEDERAL REGISTER*. For certain responsibilities comment may be solicited. Because procedures by which policies will be developed at the national and local levels are of key importance, notice for major policy initiatives is required. I believe the reorganization of Part IV achieves that goal.

**Application to the Private Sector.** Several commentators spoke on the application of the NIH guidelines to the private sector. Specifically, the NIH was urged to provide, voluntarily, to the private sector, the following:

- Advice on interpretation of the guidelines;

- Registration of projects;

- Certification of host-vector systems;

- Advice on the operation of institutional biosafety committees; and

- Protection for patent and proprietary information.

Prior to the release of the guidelines in June 1976, representatives of private industry were invited to NIH to be briefed on the guidelines. Since the release of the guidelines, several other meetings with representatives from the private sector have been held. Commerce Department representatives on the Interagency Committee



played a lead role in working with private industry leading to the agreement of relevant industries to abide by the safety standards of the NIH guidelines.

Many of the services provided by the NIH to its grantees and contractors had not been extended to the private sector. After carefully considering the comments at the public hearing and in correspondence received, I now believe the NIH should extend certain services to the private sector in several of the areas suggested by the commentators. A new section has been added to Part IV that provides the opportunity for private industry participation in a voluntary fashion. If legislation is enacted, the NIH Guidelines will serve as the basis for regulation that will encompass the private sector.

**Occupational and Environmental Safety.** A key concern of all commentators was the need for programs in occupational and environmental safety, that would include health surveillance for laboratory personnel and the community. As I stated in my Decision in 1976, the NIH has a special responsibility for national leadership in programs for laboratory safety. This responsibility is a critical one and we must accept it. Recombinant DNA research policies have stimulated a broad NIH commitment and interest in laboratory safety. The PRG-NIH reflects that commitment. As previously described, there are several training programs that the NIH has undertaken and supported. Several NIH committees are involved in development of policies in this area. The newly updated and expanded supplement to the PRG-NIH entitled, "Laboratory Safety Monograph," reflects the growing experience in this area.

A collaborative effort has been initiated between NIH and the Center for Disease Control (CDC) to establish a mechanism for providing advice, consultation, and if necessary, assistance regarding major accidents in laboratories involved in recombinant DNA research. It was not considered necessary to have a standing "strike force" as suggested by one commentator; however, in the event of an emergency, a team of experts from NIH and CDC could be formed to respond, depending on the nature of the problem.

Several commentators suggested that the NIH examine laboratory work involving genetic techniques other than recombinant DNA research. Indeed, it was recommended that another advisory committee akin to the RAC be established to propose standards for work involving biosafety, generally. I appreciate and understand this concern. The NIH over the past year and a half has created several internal committees that are critically examining different areas where labo-

ratory work is conducted with potential biohazards. These committees are considering possible recommendations for safety standards.

Another commentator also urged the NIH to consider a forum for dealing with social issues related to "genetic engineering." The NIH responsibility to date has been in addressing policy questions involving safety of recombinant DNA research in single cells in the laboratory. I recognize the importance of the potential future application of this and other genetic research to the altering of the genetic character of higher forms of life including man. However, the application of this research to the "genetic engineering" of man is clearly far from imminent. In light of public concern, a study is warranted of the ethical, legal, and social implications of these techniques. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral research considered, but was unable to initiate, a study because of its pressing workload. Such a study, however, should be a key priority for the Commission currently being considered by Congress as part of the legislation to regulate recombinant DNA research.

It has also been suggested that the NIH work closely with other relevant research and regulatory agencies, particularly the Environmental Protection Agency and the Occupational Safety and Health Administration. Indeed, the NIH, from the inception of the Guidelines, has worked to foster cooperation among the Federal agencies. Prior to the release of the Guidelines, representatives from several agencies met at the NIH for a briefing on the Guidelines. After the release of the Guidelines, the question of their extension to the rest of the Federal Government and the private sector prompted the creation of an Inter-agency Committee. This Federal Inter-agency Committee on Recombinant DNA Research on which I have served as Chairman, was created by the Secretary of HEW at the request of the President in October 1976. It is composed of all relevant Federal research and regulatory agencies and has provided for coordination of Federal policies concerning recombinant DNA research. In March 1977, the committee developed recommendations for legislation.

It was suggested by a commentator that the NIH address the international implications of control of recombinant DNA research. Indeed, the Federal Interagency Committee issued in November 1977 a thorough and comprehensive review of all guidelines for such research internationally with recommendations for continued cooperation. This report is available from the

Office of Recombinant DNA Activities, NIH, Bethesda, Md. 20014.

#### *Responsibilities of NIH (Specific)*

**Office of the Director.** As suggested by the commentators, for purposes of clarity, the responsibilities of the NIH Director have been grouped under a specific heading in the PRG-NIH entitled "Office of the Director, NIH." These responsibilities (many of which are mentioned in Parts I, II, and III of the PRG-NIH, and are repeated again in Part IV) include: final interpretation of the Guidelines; revision and amendment of the Guidelines; certification of new host-vector systems; promulgating and amending a list of classes of recombinant DNA molecules to be exempt from the Guidelines; permitting specific exceptions to the Prohibitions in the Guidelines; approving changes in containment levels for specific experiments; designating certain agents which are listed as Class 2 agents, as Class 1 agents for the purposes of the Guidelines; and overseeing the implementation of the Guidelines. For many of the responsibilities, appropriate notice and opportunity for public comment will be provided.

**Recombinant Advisory Committee.** At the hearing in 1976, many commentators made suggestions concerning the structure, function, and scope of responsibility of the RAC. Comments on possible structural mechanisms for decision-making included suggestions that there be a scientific and technical committee and a general advisory public policy committee. It was also suggested that the scientific committee include scientists who are to actively engaged in recombinant DNA research, and that the public policy committee have a broad scientific and public representation. In response to those suggestions in 1976, the roles of the RAC and the NIH Advisory Committee to the Director (DAC) were spelled out. The RAC responsibility has been primarily a scientific and technical one with recommendations for revisions of the Guidelines reviewed by the DAC, the public advisory group. In the main, that process has worked well over the past 1½ years and its structure is maintained in the PRG-NIH.

I am acutely aware of the need for broad scientific representation on the RAC, and I have carefully considered these needs in the selection of new members. The emphasis has been to ensure relevant scientific representation. It is absolutely essential that this committee have the technical expertise necessary to develop, modify, and interpret the Guidelines based on scientific evidence. Additional representatives have been added from scientific disciplines, such as botany, to ensure a broad scientific overview. As a bridge



between the scientific and the public policy implications, public members now serve on the RAC and additional public members may be added. Current public members are Dr. Emmette S. Redford, Ashbel Smith Professor of Government and Public Affairs, Lyndon B. Johnson School of Public Affairs, University of Texas at Austin; and Dr. LeRoy Walters, Director, Center for Bioethics, Kennedy Institute, Georgetown University. Both have served the public interest well and have done a superb job as have all members of the committee. The task for all RAC members has been enormous and their work and spirit of cooperation have been exemplary.

In order to ensure fairness, and sensitivity to the public commentators, solicitation of nominations for openings on the RAC will be in accord with the recommendations of the NIH Grants Peer Review Study Team concerning announcements of vacancies on committees. Thus, NIH will publish, periodically, an announcement of upcoming vacancies on the RAC with instructions on how to submit nominations. By this means I will be able to consider carefully a wide spectrum of nominations and assure appropriate representation suited to the needs of this committee.

One commentator suggested that representatives from Federal agencies serve on the RAC. Several agencies, including the National Science Foundation, the Department of Energy, and the Department of Agriculture, have liaison representatives who come regularly to the RAC meetings and, of course, the Federal Interagency Committee is kept fully informed of the activities of this committee.

It was also recommended by a commentator that the NIH finance the cost of attendance at RAC meetings by interest members of the public. For the present I do not believe such a policy is necessary, especially in light of the responsibilities of the DAC for public oversight where public witnesses may be invited and their expenses paid (as they were at the December 1977 hearing). All RAC meetings are announced in the *FEDERAL REGISTER* and are open to the public.

In sum, the operations of the RAC have been more clearly detailed in the PRG-NIH. The procedures for the selection of members and the operations of the committee have been, or are in the process of being, formalized for the benefit of the scientific community and the public.

**NIH Components.** A new section now describes all other functions of the NIH including the responsibilities of the Office of Recombinant DNA Activities (ORDA). Several commentators at the public hearing in 1976 urged that the NIH create an office to co-

ordinate recombinant DNA activities. On the basis of these suggestions, ORDA was created and Dr. William Gartland was named Director. Since its creation, ORDA has done a splendid job in fulfilling very difficult tasks in the implementation of the NIH Guidelines. Dr. Gartland, who also serves as Executive Secretary to the RAC, has provided a focus for coordination of activities within the NIH and with institutional biosafety committees.

It is important to note that the responsibility of the NIH peer review groups (e.g., study sections) for an independent assessment of the recombinant DNA research protocols has been eliminated. This responsibility will now solely be that of ORDA in conjunction with the institutional biosafety committee. In the 1½ years of our experience, such review by NIH peer review groups has been found to be unnecessary and an additional burden on these groups.

Several commentators urged new responsibilities for ORDA and additional personnel to fulfill them. Several urged that ORDA be responsible for inspecting and certifying laboratories at the P3 level. At the present time P4 facilities are operating at the Frederick Cancer Research Center in Frederick, Md, and at the NIH in Bethesda, Md; no other P4 facilities for recombinant DNA research are in operation nationally. The NIH has the responsibility under the Guidelines to certify P4 facilities because of their special nature. However, a P3 facility does not require special expertise at a national level; and there is no need for national certification of P3 facilities. As specified, the local institution has responsibility for monitoring and certifying facilities from the P1 to the P3 level and that, indeed, should be a local responsibility.

Several commentators urged greater dissemination of information to the public and scientific community alike. ORDA has a key responsibility for the dissemination of information through the "Recombinant DNA Technical Bulletin." The Bulletin is a new publication that attempts to link investigators involved in recombinant DNA research, both in the United States and abroad, with the advisory groups and organizations active in this area. In light of comments received, the Bulletin will include more information for institutional biosafety committees, as well as for the advisory groups at the national and local levels. It was suggested that ORDA provide advice to state and local governments, and to the most practical extent, ORDA will be available to state and local governments for technical advice. In large part, ORDA serves as a clearinghouse for information related to recombin-

ant DNA activities internationally, nationally, and locally.

#### *Registration and Compliance (General)*

Over the past 2 years in the administration of the NIH Guidelines, it has been clear to me that a new section should be added on the general requirements for registration of activities with the NIH, not only for NIH grantees or contractors, but also, on a voluntary basis, for the private sector. Further, in light of the review of HEW policies on the patenting of recombinant DNA research inventions, a section on disclosure of information was also necessary. And finally, as suggested, a section on compliance with the Guidelines was needed. Thus, new sections C and D have been added under "Roles and Responsibilities" covering Registration (including disclosure of information) and Compliance. Many comments on the Guidelines over the past 1½ years and at the public hearing in December 1977 urged that these provisions be added, and in my view, they are necessary in the absence of legislation. Further, if legislation were to pass, these provisions could serve as a model for the regulations to be promulgated on the basis of the legislation. As in 1976, I believe the Guidelines should not become regulations without new legislation specifically mandating this.

#### *Registration and Compliance (Specific)*

Section IV-C has been added providing the elements for registration. Other requirements may need to be added; notice will be given of any change in the requirements. All projects subject to the Guidelines must be registered with ORDA. A mechanism for voluntary registration by the private sector has been provided in response to suggestions by private sector representatives. A requirement for registration is that the registrant must agree to abide by the standards of the Guidelines.

Many comments were directed to the protection of proprietary information. A new section outlining the elements for protection of proprietary data has been included in response to these suggestions.

One commentator urged that no patents be granted for recombinant DNA research inventions. Shortly after the release of the Guidelines in 1976, NIH received a letter requesting a review of HEW policies relating to the patenting of recombinant DNA research inventions. The letter prompted NIH to review current patent regulations governing existing institutional patent agreements and to consider how recombinant DNA research inventions should be handled under the terms of those agreements. On the basis of ex-



tensive Department and Interagency Committee review, it was agreed that, at least for the present, recombinant DNA research inventions developed under HEW/NIH support should continue to be administered within current HEW patent agreements. Each agreement, however, would require that licenses could be granted only if the licensee provides assurance of compliance with the physical and biological containment standards set forth in the Guidelines. My decision and analysis on this were released in March 1978. A copy is available from the Office of Recombinant DNA Activities, NIH, Bethesda, Md. 20014. Thus, I do not believe that a restriction of patents in this research area is warranted.

A commentator urged that a system of fines be spelled out. NIH has no authority to impose fines in the absence of new legislation. However, NIH will suspend, limit, or terminate a grant or contract for noncompliance with the Guidelines. A commentator urged that penalty procedures be specified. Should it be necessary to suspend, limit, or terminate a grant, appropriate HEW procedures will be followed.

In sum, Part IV of the Guidelines on Roles and Responsibilities has been substantially revised in response to the suggestions from many commentators. The Guidelines now provide even more opportunity for advice from the local to the national level. The spirit of cooperation and effective oversight will be enhanced by the revised Guidelines both at the local level between the research community and the public and at the national level with Federal agencies, the scientific community, and private sectors.

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# RECOMBINANT DNA RESEARCH—REVISED GUIDELINES PROPOSED BY THE DIRECTOR, NIH

JULY 1978.

## TABLE OF CONTENTS

### I. Scope of Guidelines.

- I-A. Purpose.
- I-B. Definition of Recombinant DNA Molecules.
- I-C. General Applicability.
- I-D. Prohibitions.
- I-E. Exemptions.
- I-F. General Definitions.

### II. Containment.

- II-A. Standard Practices and Training.
- II-B. Physical Containment Levels.
  - II-B-1. P1 Level.
  - II-B-1-a. Laboratory Practices.
  - II-B-1-b. Containment Equipment.

### II-B-1-c. Special Laboratory Design.

#### II-B-2. P2 Level.

- II-B-2-a. Laboratory Practices.
- II-B-2-b. Containment Equipment.

#### II-B-2-c. Special Laboratory Design.

#### II-B-3. P3 Level.

- II-B-3-a. Laboratory Practices.
- II-B-3-b. Containment Equipment.

#### II-B-3-c. Special Laboratory Design.

#### II-B-4. P4 Level.

- II-B-4-a. Laboratory Practices.
- II-B-4-b. Containment Equipment.

#### II-B-4-c. Special Laboratory Design.

### II-C. Shipment.

### II-D. Biological Containment.

#### II-D-1. Levels of Biological Containment.

##### II-D-1-a. HV1.

##### II-D-1-b. HV2.

##### II-D-1-c. HV3

#### II-D-2. Certification of Host-Vector Systems.

#### II-D-3. Distribution of Certified Host-Vectors.

### III. Containment Guidelines for covered Experiments.

#### III-A. Classification Of Experiments Using the *E. coli* K-12 Host-Vector Systems.

##### III-A-1. Shotgun Experiments.

##### III-A-1-a. Eukaryotic DNA Recombinants.

###### III-A-1-a(1). Primates.

###### III-A-1-a(2). Other Mammals.

###### III-A-1-a(3). Birds.

###### III-A-1-a(4). Cold-Blooded Vertebrates.

###### III-A-1-a(5). Other Cold-Blooded Animals and Lower Eukaryotes.

###### III-A-1-a(6). Plants.

##### III-A-1-b. Prokaryotic DNA Recombinants.

##### III-A-2. Plasmids, Bacteriophages, and Other Viruses.

##### III-A-2-a. Viruses of Eukaryotes.

###### III-A-2-a(1). DNA Viruses.

###### III-A-2-a(2). DNA Transcripts of RNA Viruses.

###### III-A-2-a(3). Intracellular Viral DNA.

##### III-A-2-b. Eukaryotic Organelle DNAs.

##### III-A-2-c. Prokaryotic Plasmid and Phage DNAs.

##### III-A-3. Lowering of Containment Levels for Characterized or Purified DNA Preparations and Clones.

### III-B. Experiments with Other Prokaryotic Host-Vectors.

### III-C. Experiments with Eukaryotic Host-Vectors.

#### III-C-1. Vertebrate Host-Vector Systems.

#### III-C-2. Invertebrate Host-Vector Systems in Which Insect Viruses Are Used to Propagate Other DNA Segments.

#### III-C-3. Plant Viral Host-Vector Systems.

#### III-C-4. Plant Host-Vector Systems Other than Viruses.

#### III-C-5. Fungal or Similar Lower Eukaryotic Host-Vector Systems.

### III-D. Complimentary DNAs.

### III-E. Synthetic DNAs.

### IV. Roles and Responsibilities.

#### IV-A. Responsibilities of the institution.

##### IV-A-1. Institution.

##### IV-A-2. Institutional Biosafety Committee.

##### IV-A-3. Biological Safety Officer.

##### IV-A-4. Principal Investigator.

#### IV-B. Responsibilities of the NIH.

##### IV-B-1. Office of the Director, NIH.

##### IV-B-2. NIH Recombinant DNA Advisory Committee.

##### IV-B-3. NIH Components.

#### IV-C. Registration.

##### IV-C-2. Voluntary Registration and Certification.

##### IV-C-3. Disclosure of Information.

##### IV-D. Compliance.

##### IV-D-1. Policy on Noncompliance.

### V. Footnotes and References.

#### I. SCOPE OF THE GUIDELINES

**I-A. Purpose.** The purpose of these guidelines is to specify practices for constructing and handling (i) recombinant DNA molecules and (ii) organisms and viruses containing recombinant DNA molecules.

**I-B. Definition of Recombinant DNA Molecules.** In the context of these guidelines, recombinant DNA molecules are defined as either (i) molecules which are constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell, or (ii) DNA molecules that result from the replication of those described in (i) above.

**I-C. General Applicability.** The guidelines are applicable to all recombinant DNA research within the United States or its territories conducted at or sponsored by an institution that receives any support for recombinant DNA research from NIH. This includes research performed directly by NIH.

Any individual receiving support must be associated with or sponsored by an institution which can and does assume responsibilities described in these guidelines.

Once approved at the local level, research may proceed but shall be modified in accordance with the recommendations of the NIH if found not to

## A SCIENTIST'S VIEW OF PRIORITIES AND CONTROL IN THE ORGANIZATION OF RESEARCH

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Science, as a method of interpreting or understanding the universe we inhabit, has no logical boundaries in time or geography. Nevertheless, science has always been, and continues to be, firmly anchored in the political, cultural and other rules of the society in which it operates. Despite its present and potential powers, science must operate in accordance with societal law and cannot be above it.

I know of no serious scientists who believe that this circumstance could or should be otherwise. Arguments for the absolute sovereignty of scientific inquiry have been laid to rest.

There are instances, however—and the record of this Symposium will contain many of them—when the interdependence of science and modern society will be decried by one party or the other. But recognition of their intertwined fates—and acceptance of these arrangements as good and appropriate, if not without major problems—is where my discussion must begin.

How, then, from a scientist's point of view, should science and society divide responsibilities in this mutually essential collaboration?

Some scientists may be concerned about the purity of my presentation of their case. Having migrated in recent years to the interface between research and other health missions, I am potentially corrupted by intensive exposure to the demands made upon science by political, legal and other social institutions. On the other hand, since I was long a practitioner and am now a highly placed administrator of very 'big science'—the head of an agency which supplies almost half of all government research support to American universities—I appear no less suspect to the critics of science as being incapable of objective analysis of my fellow scientists.

If there is no way out of this dilemma, we can both be comforted: you by a handy explanation for any differences in our points of view, and I by the belief that, like certain detergents, I may reduce some interfacial tension without losing my integrity in the process.

Let us look at the basic equation of interdependence.

First, a truism: Society supports science not because it sees science as good in itself, but because it expects certain practical benefits from its investments. 'Science in human service' is the theme. The anticipation of benefits may be long-term or short-term—more often the latter. But without the anticipation—and without demonstration of success from time to time—societal support for science would dissolve. And experimental science, now almost totally dependent on collective support, would then stagnate.



Despite negative views from a number of critics, no public opinion polls that I know of have indicated that the average citizen finds achievement in the natural sciences to be falling seriously behind expectations. The United States, enamoured of the technologies which have both enriched and corrupted all affluent countries, maintains a political consensus which supports large-scale investment in research. This is true even when expectation of benefits must be deferred to the long-term, as in much of health research<sup>2</sup>.

A closer look at societal patronage of science is warranted.

In any society today, the ultimate 'control' of science falls to those who provide the necessary material resources. In the United States, as in most countries, the dominant source of science support is the State. For example, in biomedical research, the federal share of the total is about 60%; the role of private industry and private philanthropy is still important but is clearly subordinate<sup>3</sup>. This means, of course, that the opportunity for control or governance of science has fallen into the hands of the public—and so has the responsibility for the nurture of the enterprise.

I do not regard the aggregation of the support of science into a single source, whether it be government or non-government, as a good thing. Multiple sources assure plural approaches and more flexibility. The potential weakness of government monopoly of support is not the ultimate control by the public but bureaucratic stultification or political manipulation. Given the inevitable participation of public patrons in the overseeing of science, I have certain views on the appropriate loci and nature of controls within the numerous jurisdictions and divisions of government.

In most countries, the dominant role usually resides in the largest division, or 'central' government. But there are some interesting and important variations on this theme. In the Federal Republic of Germany, the *länder*, or states, provide most of the support for the universities; and, hence, an unusual degree of decentralization exists in the maintenance of research capability. In Canada, several provinces dedicate certain revenues to research; and their budgets are large and in some ways competitive with Dominion (Medical Research Council) support. In the case of the United States, as noted previously, support is derived overwhelmingly from the federal government.

In times of affluence, when competition for societal funds is not so intense, there are few disadvantages and many advantages to the funnelling of public support of research mainly through the apparatus of the central government. Better balancing of effort, better adjustment of major priorities in line with social needs and technical opportunities, and greater stabilization of the scientific system are all possible. To these can be added the employment of the maximum technical expertise and, in the best of circumstances, the minimum exercise of parochial political interference in the selection of which scientists and which ideas will be awarded the government's support.

To the scientist, this latter point is crucial: there needs to be a reasonable basis for confidence in the objectivity of support decisions. A fair degree of reassurance on this objectivity is one of the advantages enjoyed by the National Institutes of Health (NIH), with its peer review system, since federal support became significant in the 1940s. The making of decisions at a single bureaucratic locus, remote from the institutions, becomes acceptable when a better quality of review of ideas is made possible by such central determination. And, basically, this type of competitive review, carried out by scientific peers, *cannot* be replaced among the criteria for deciding who gets public

support for scientific work. It can be, and is, supplemented by other criteria, in which lay or nontechnical values also play an essential part.

In regard to other aspects of 'control', or regulation of experimentation, the political locus is perhaps an even more important issue. The federalist controversy (over the appropriate division of powers between the central government and component states) is a long and involved constitutional matter in the United States<sup>4</sup>. It has only recently been interjected into the regulation of laboratory or clinical science. Here, I think, most American scientists are of two minds about federalism; there is

(1) a desire to have the largest scientific community, or the maximum of expertise, involved in collective criticism and judgement in the setting of uniform standards—a strong 'federalist' position; but there is also

(2) a strong desire for self-governance by the scientists and their institutions in applying those standards—an antifederalist and pro-home-rule position.

These markedly ambivalent sentiments were experienced by many American biologists during our recent developmental work on guidelines for use of recombinant DNA techniques.

Attempts to regulate basic science in the laboratory, in order to immunize against hypothetical risks, are fraught with peril; the alarm may—and should—be raised by conscientious scientists, but the ensuing debate will be exploited by some who are attracted to it for selfish purposes. If it appears that uniform rules are needed to protect life and property until key questions are clarified, the best qualified and most balanced of expert opinions must be sought in the widest possible sampling. Because science is so universal a process, these problems are transnational matters; their solutions are awkwardly interrupted, even by national boundaries, although nations are the largest jurisdictions in which uniform legal authority can easily be exercised today.

We have witnessed, in the recombinant DNA matter, a number of instances in which political subdivisions of the United States debated the enjoining of intellectual inquiry, as though it were a stream-polluting factory or an inflammable storage tank. Some of these actions appear to have been initiated for small and private purposes. After what was often prolonged and confusing debate, the storms usually dissipated in a resurgence of public wisdom and good sense.

In the light of my own personal experiences in this area, I would maintain that the only valid criterion for interference with laboratory science by small jurisdictional elements (states, provinces, countries, towns) is the presence of *demonstrable* risk. Indeed, a societal taboo must be maintained that resists capricious local interference with scientific or intellectual inquiry on any basis other than imminent hazard to life or property.

The initial request of the scientists for federal assistance in creating guidelines did not anticipate the heavy procedural tax that accompanies any federal intervention<sup>5</sup>. This levy includes the often cumbersome procedures, the expense and the delays involved in promulgation, review and revisions of regulations in an honest attempt to keep the public involved in the process. Even when guidelines that have something less than the force of laws are the vehicle of regulation, due process must be protected at the expense of greater inertia in the system.

Let me return to the scientists' views of setting priorities in science: a means of fiscal control. As an example, I will use that part of the research enterprise with which I am most familiar—biomedical research as it is supported in the United States.



Although most research is carried out in universities, the federal government—which includes both Congressional and Executive branches—in fact determines many things about that research. These include: the overall size of the research effort; the agencies and specific mission assignments by which main social purposes are served through research; the broad structure of national priorities, as reflected in differential resource allocations to the various science appropriations; and the terms and conditions under which resources are made available to research agencies, collaborating institutions and individual investigators.

Moreover, in the support of biomedical research, there is a notable trend towards closer control—more intense overseeing—by public patrons. This phenomenon is clearest in Congress, which over the years has been a stronger advocate of health research than the Executive branch.

Ten years ago, NIH research programmes, with very minor exceptions, were supported by broad legislative mandates without time or dollar limits. Today, in a pattern set by the National Cancer Act of 1971, two-thirds of NIH programme funds are tied to detailed statutes. Typically, these will set programme funding ceilings for one-, two- or three-year periods and may require quite specific programme elements, such as multipurpose research centres or community outreach activities.

These multiplying mandates are generated by groups of public advocates, who urge upon the Congress the setting of special priorities for particular disease or health problems. Such activities force science to account for its failures and to prove its concern with human distress. They may also bring forth more support; but 'side effects' are not uncommon. The mandate may come for areas where more useful research cannot be carried out, or where new funds are not provided for new efforts, so that one programme loses as another gains.

Other elements broaden public overseeing of health research well beyond mere fiscal control. For example:

(1) New sets of Congressional committees have taken keen interest in NIH programmes, as the health relevance of environment and nutrition issues has gained new credibility.

(2) Government-wide legislation aimed at issues apparently remote from research—such as freedom of information and privacy—has in fact made a sharp impact on traditional ways of managing research.

(3) We note rising public demands that new technologies—the results of research programmes—be assessed for economic, ethical and other social implications. Public pressures for broadened research missions and the acceptance of new types of responsibilities by members of the research community grow visibly.

(4) In the regulatory mode, a growing body of legislation and administrative law has further changed the context of research programme management. We may cite here regulations of various kinds for the protection of human research subjects, the National Environmental Protection Act, the Toxic Substances Control Act and the Occupational Health and Safety Act.

Most scientists are able to see that many or most of these new requirements or expectations are not unreasonable. It is part of the accountability of the scientist for his use of social capital. But there is one incontrovertible fact: new regulations add to the complexity of the cost and management of research.

There is also a limit to *effective* public participation in the allocation of resources for

research. I do not know whether we have reached it in the United States. At the least, we are close.

The creative engine of science can be fuelled by governments but cannot be ignited by them. Research, by definition, is inquiry into the unknown. But the unknown cannot be perfectly programmed, nor discovery scheduled. One learns to discount the ready belief that difficult research goals will be achieved if only more resources are added or management is improved.

A major source of tension between scientists and a number of their social critics is the degree to which the research project should be 'investigator-initiated', as opposed to being predetermined by some adaptation of systems management or 'matrix' organization. An extreme belief in 'free enterprise' by individual scientists, working alone on precisely what they choose, is an anachronism. It overlooks the degree to which aggregation of effort by researchers in teams, supported by sophisticated instruments, is required for achievement in today's research. An excessive faith in external programming, on the other hand, ignores the still intensely personal dynamic of the quest, the individual researcher's need for his own synthesis of the hypothesis to be tested, the method of test and probabilities of success. The drives for gratification of the 'selfless' scientist are complex, but their essentiality in the process is the one irreplaceable control that scientists still have over research.

My view, in sum, is this: the principal role of central administration should be the maintenance of a healthy balance of resource distribution, the development of processes for determining excellence in research ambition and achievement, and the fostering of communications among scientists and between science and society.

Let me turn again to the biomedical sciences in the United States. For twenty years, government and science collaboration in this area has been effective and mutually beneficial. Yet, today, many thoughtful observers see this relationship as in a state of transition. Competition for federal resources in health and other areas increases as economic difficulties persist and self-imposed limits on Congressional appropriations become effective. Inflation and the rising rate of indirect costs further erode net programme support. And we have already noted the complexities for management and the drain on resources implicit in certain growing pressures on the research community. These include pressures for expanded research missions and the assumption of new tasks. They also include the rising imposition of administrative law and regulation, with all of the limiting impacts on science initiatives that these imply.

The ability to sustain the present capacity for scientific research in the United States (and perhaps other countries as well) is now uncertain. A downward shift in public support of health research will bring new tests of how this endeavour shall be controlled and priorities set. It will require careful judgements on which are the most essential elements to be sustained through an uncertain period.

I have previously stated that were the research budget to be drastically reduced, we should consider our last line of defence to be the support of the most creative investigators to pursue their own ideas<sup>6</sup>. This is perhaps a frivolous suggestion, for such extreme conditions are not going to occur.

No, the first priority in adapting to *cessation of expansion* of research capacity is to sustain the vitality of the institutions in which most of the research is carried out, that is, the universities, and the government laboratories (the national labs), which can carry out research in some ways more efficiently than the universities. At the same level of



priority is the need to sustain the capability for competitive assessment of excellence among investigators, including their choice of problems and proposed lines of attack.

Secondly, we need to assure stable support for that broad body of basic and most applied research that constitutes the science base for further knowledge development. Investigator-initiated portions of this research warrant first priority. As part of this, add the need to make sure that some portion of research resources is made available each year to new investigators entering health research; that appropriate training is afforded the next generation of research investigators; and that sensitive annual adjustment of resources is made among science base activities, to respond to shifts in research opportunities and needs.

The task of government in properly allocating scarce resources to science is increasingly onerous. The Secretary of Health, Education and Welfare in the United States has found the problem to be so demanding that he has called for a national consensus on the principles that should underlie long-range planning for the future<sup>7</sup>.

As the chairperson appointed to guide this first synthesis of principles, I must retain an open mind as to the outcome. I hope, however, that within the fabric of such principles there will be visible the following threads:

(1) Science is both a body of knowledge and a process dedicated to serving man. The continuity and durability of science is a human, a *public*, responsibility.

(2) The public must be aware of the limitations of science in solving human problems; at the same time it should have a fair appraisal of the past achievements and the future potential of science. It must learn to understand, to choose and to use prudently the technological creations of science. No other acceptable way exists to control the outcome of an incessant search for knowledge.

(3) Scientists must be responsible for the technical side of a partnership with laymen in the use of science. The scientists should not yield their role in estimating what science can or cannot accomplish; nor can they shirk their responsibility to foresee and explain the implications of new discoveries. Theirs is a tremendous responsibility: to be highly accountable, true to the internal ethic of their discipline, yet humane. One hopes that they will always have room, as well, for optimism.

(4) While one speaks of 'society' and of 'the public', it is government which serves as the ultimate mediator between science and the other elements of society. May much wisdom be given to the agencies and institutions of government in their future relationships with science. Respective roles need to be understood and sustained. In no context is this more important than in the incipient rise of new laws and regulations over the experimental sciences.

Over the past several years, I have had occasion to consider the law and science, particularly in the context of regulating the use of recombinant DNA technologies. I have included in my reading much of Oliver Wendell Holmes and some of the scientific philosophy of his contemporary, Charles Sanders Peirce. One source in which their views are mentioned together is a set of lectures by the Yale professor of law, Grant Gilmore, which are reproduced in *The Ages of American Law*<sup>8</sup>. He ends this book with a paraphrase of Holmes—one that expresses my own feelings about the application of much of statutory regulation to research:

'Law reflects but in no sense determines the moral worth of a society. The values of a reasonably just society will reflect themselves in a reasonably just law. The

better the society, the less law there will be. In Heaven there will be no law, and the lion will lie down with the lamb.

'The values of an unjust society will reflect themselves in an unjust law. The worse the society, the more law there will be. In Hell, there will be nothing but law and due process will be meticulously observed'.

This view of the place and value of law underscores the importance of the topic of this Symposium, 'Ethics for Science Policy'. Certain kinds of people are attracted to science, a process which frees their minds but increases the need for self-criticism and conscientious restraint. The scientist is largely rewarded by recognition. This in turn requires full communication and submission both to collective criticism by peers and to prevailing ethical standards, enforced through constraints upon his continued support by society. No law, inspection force or other external regulation can protect the public and the experimentalist alike from untoward effects of science like responsible and responsive self-governance of that process. This kind of self-determination is the ultimate test of the ethical basis of science.

#### Notes

1. National Science Foundation (1978) *Federal Funds for Research and Development for Fiscal Years 1977, 78, and 79*, 27, Appendix C, Table C-10, Washington DC (NSF 78-312). In fiscal year 1977, the National Institutes of Health provided \$1.2 billion of the \$2.6 billion total federal research and development support to higher educational institutions.
2. Office of Management and Budget (1978) *Special Analyses: Budget of the United States Government, Fiscal Year 1979*, Table P-12, Washington DC, p. 329. This analysis shows a steady upward trend in federal research and development funding, from \$3 billion in 1953 to \$26.3 billion in 1978, except for minor decreases in the years 1969 to 1971.
3. National Institutes of Health (1978) *Basic Data Relating to the National Institutes of Health—1978*, Washington DC (NIH 78-1261). Data for 1977 show that the federal share of health research and development was 61% of the total, that of industry 29% and that of private philanthropy less than 10%.
4. Gilmore, G. (1977) *The Ages of American Law*, New Haven and London, Yale University Press, p. 93. This is an interesting and useful discussion of 'federalism' issues.
5. National Institutes of Health (1978) Proposed revised guidelines for recombinant DNA research. *Federal Register*, July 28, Part IV, p. 9. See discussion in 'Introduction and Overview'.
6. Fredrickson, D. S. (1977) Health and the search for new knowledge, *Daedalus*, 106, Winter, p. 164.
7. Califano, J. A., Jr (1978) *Remarks Before the Annual Meeting of the American Federation for Clinical Research, San Francisco, California, April 29, 1978*, Washington DC, Department of Health, Education, and Welfare.
8. *Op. cit.* note 4.
9. *Ibid.*, p. 111.



## REMARKS FOR MOREHOUSE COLLEGE CONVOCATION\*

by

Donald S. Fredrickson, M.D.\*\*

President Gloster, Dean Sullivan, honored guests, members of the faculty (members of the inaugural class):

I am pleased and honored to represent Secretary Joseph A. Califano, Jr., and to extend to you his hearty congratulations on the achievement signified by this ceremony and to express to you his deep interest in the future growth and success of the School of Medicine at Morehouse College. It is a pleasure and honor for me to be his representative at this Convocation, because all of us who, like the Secretary, are committed to improvement of health care for ALL of the American people recognize the importance of what is happening here and strongly feel that history is being made.

Morehouse College is nationally recognized for its excellence. It is known for its tradition of producing Black leaders and scholars. The significant program now being launched is an extension of that tradition into another and vital area of service to human needs.

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\* Held on Sunday, September 10, 1978, in Atlanta, Georgia.

\*\* Director, National Institutes of Health, Bethesda, Maryland 20014.

As the first predominantly Black medical school to be developed in this country, you have an unusual distinction, and with it heavy responsibility. But the soundness of your planning, and the able and persistent efforts of your leaders, have justified and attracted the Federal, State, and private support essential to the establishment of the School of Medicine at Morehouse College. I have confidence that the quality of leadership which has been demonstrated together with your future achievements will assure the continued development and sound growth of this institution.

Your stated purpose to educate more physicians to serve the minorities, and the medically-indigent will help to redress a persistent, serious imbalance in the Nation's health care. The merit of this concept is illustrated by a study, soon to be published and upon which Secretary Califano commented in an address to the National Medical Association last August. The study reveals that among Black graduates of your sister institution, Howard University, 93 percent serve some Black patients and 72 percent provide care to a patient population that is largely Black. Among Howard students and practicing graduates, there is shared a strong desire to help the medically underserved.

The Secretary commented that, "In view of these special contributions, I believe that we must make special efforts to help traditionally Black institutions. As these institutions . . .

encounter serious financial problems -- problems that may in the short terms get worse rather than better -- they may need special help to survive and succeed."

But the message which the Secretary has asked me to give to you is firmly grounded in practical gain to the Nation and expressed in the most emphatic terms. Here are his words: "We have made great progress since the 1960's and we can make much more. It would be a tragedy indeed if the Nation having come so far in its quest for equal opportunity should now abandon or falter in its quest.

"We in this administration do not intend to falter, and we recognize that much remains to be done."

I need not tell the faculty, administrators, students, representatives of cooperating institutions, and many interested friends of the School of Medicine at Morehouse College that you have accepted an exciting and demanding challenge. I am certain that you will meet it worthily, with success and to the continuing benefit of the health of future generations.

## REMARKS\*

by

Donald S. Fredrickson, M.D.\*\*

BUENOS DÍAS SEÑORAS Y SEÑORES

CÓMO SIEMPRE, ES UN GRAN PLACER PARA MI TENER LA OPORTUNIDAD EN TOMAR PARTE EN ÉSTAS FUNCIONES QUE NOS RECUERDAN QUE ÉSTE GRAN PAÍS TIENE MUCHAS RAÍSES QUE LE HAN AYUDADO A SU GRANDEZA. UNA DE LAS MÁS PROFUNDAS RAÍSES ES LA DEL HISPANO.

LADIES AND GENTLEMEN, as I said in Spanish, it is always a pleasure to take part in these functions which remind us that this grand Nation has many roots which have helped make it great. One of the deepest is that of the Hispanic.

In understanding our neighbor, he becomes our brother. These programs are arranged not only for our enjoyment, but to give us insight into the history and culture of our Hispanic American brothers. Thank you for being with us. I know you will enjoy the program.

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\* Presented at Hispanic Cultural ceremonies at NIH in the Masur Auditorium on Thursday, September 14, 1978.

\*\* Director, National Institutes of Health, Bethesda, Maryland 20014.



## HEALTH SCIENCE: THE PROMISE AND THE PROBLEMS\*

by

Donald S. Fredrickson, M.D.\*\*

Walt Whitman once observed that, "It is provided in the essence of things that from any fruition of success - no matter what - shall come forth something to make a greater struggle necessary."

This is generally true of science and the technology derived from it. And nowhere has this paradox been more visible in the past few years than in the health sciences. Here the successes of the recent past have brought us not only the promise of further accomplishments, but also fathered new problems. The greater is the momentum of discovery, the brighter is the penumbra of the complex companion issues that must be untangled and solved to make the victory complete.

For some peculiar reason, it occurs to me at this very moment that nuclear medicine is a superb example of achievement in health science and technology, and at the same time is also illustrative of some of its problems. From the beginnings of this subspecialty, realization has always been in hot pursuit of -- and frequently overtaken -- its potential.

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\* Presented at the Second World Congress of Nuclear Medicine and Biology, Washington Hilton Hotel, Washington, D.C., on Sunday, September 17, 1978.

\*\* Director, National Institutes of Health, Bethesda, Maryland

Nuclear medicine is almost coeval with my own career in medicine. Even while still an intern, I was helping to construct one of the early instruments used in measuring thyroid function with radio-iodine. I remember counting  $C^{14}$  in little discs of  $BaCO_3$ , and converting  $H^3$  to methane for proportional counting. In adapting the detection of  $I^{121}$  for some studies, I also recall having to make our own scintillation counter from one of the big thallium-activated sodium iodide crystals then obtainable only from the Harshaw Chemical Company in Cleveland. I was in Boston at the time and Robley Evans was giving his immensely popular course on radiation at M.I.T. It was the latest word on adapting the recently available isotopes to practical purposes -- including medical ones. I was forced to audit his course; a fair shot at passing the exam required an ability to handle Schrödinger equations. They were beyond my reach; for hastening to patch up the thinnest of war-time premedical preparations, I had only just started calculus in summer school in Cambridge. (Later it would allow me to say that my post-graduate record at Harvard was "straight A" -- one course!)

Evans was right to demand that his chemical engineers be prepared in depth to handle the enormous promise and the coming problems inherent in using radionuclides for peaceful purposes. I don't think many of us thought at the time that the biological or medical uses would soon spawn a new subspecialty dedicated solely to their exploitation. When I came

to Bethesda in the early 50's, I brought with me a fairly heavy experience in using isotopes, expertise that still was uncommon at the time. For example, Ralph Peterson and I tested the liquid scintillation counter at the Clinical Center, the first such instrument there, and only the second prototype in the world. As you now know, it became a gadget successful beyond any designer's dream. Yet, I still recall the skepticism with which I greeted the suggestion then that one could make a living by having a specialist in something called "nuclear medicine" -- or that there was a "nuclear" biology as opposed to a "Warburg" or "Lineweaver-Burk" one.

Now we can see that the rise of an independent and important discipline was inevitable. It has come into being so rapidly that its structure is still rapidly evolving - trying to catch up with its expanding functions. The range of subjects to be discussed in your scientific meetings during the coming days gives testimony to the expanding inventory of possibilities in nuclear medicine today.

You have literally added the third and fourth dimension to diagnostic imaging. And you are doing so with non-invasive techniques, a step that is unarguably in the proper direction for health technology to evolve.

Body functions have become "visible" in the living subject and in dynamic rather than static terms. New understanding of both physiology and malfunction has grown apace with this



new illumination. At the same time you have managed to diminish the amounts of ionizing radiation to which the patient must necessarily be subjected; most importantly, you have even eliminated this form of radiation in some applications through the use of ultra-sonic and infra-red imaging. Could it be that you're going "non-nuclear" so fast you'll soon devour yourself?

I'm sure the answer is negative, for no serious decline of this specialty is likely for a long time. Through nuclear medicine, the more sophisticated techniques of biology are steadily being converted to more useful and practical purposes.

The exquisitely sensitive and powerful technique of radio immunoassay (RIA) which permits analysis of the hormonal and biochemical function of biologic systems has brought about a revolution in both practical and theoretical immunology. Minute amounts of important biological substances can now be uncovered in small samples of body fluids. This dynamic description of bodily functions becomes possible through the use of sequential sampling. Once again the time dimension is added to conceptions of molecular events.

The technical simplicity of RIA and the ease with which the necessary reagents may now be obtained have been responsible for its adoption today by thousands of hospital and non-hospital clinical laboratories for a great variety of analyses. And the technique is used extensively world-wide, even in nations



whose own scientific development has had to await the solution of more pressing social problems.

The current uses of RIA have not exhausted its potential. In her Nobel Lecture, Rosalyn Yalow shared an intuition that in "the 1980's the impact of RIA on the study of infectious diseases may prove as revolutionary as its impact of endocrinology in the 1960's." She cited the start that has already been made in virology. Though infectious diseases have become less prominent as causes of death and disability because of improved sanitation and the advent of antibiotics, she correctly noted that infectious diseases "remain a major public health problem throughout the world and simple inexpensive methods of identifying carriers would facilitate eradication of these diseases."

My friend, your President, Henry Wagner, speculated in a recent article that "Perhaps we shall be able to redefine diseases and recognize them at a much earlier functional stage even before detectable structural changes have occurred."

This week I, too, felt the fever of infectious optimism as I listened to a lecture of "Receptor Disorders in Man" by Jesse Roth. Today the power for exploring unknown territory in biology is extraordinary. Vastly greater than it was even 25 years ago. Perhaps it is like comparing the capacity of an explorer satellite to the relatively feeble compass and astrolabe of Prince Henry the Navigator. Even this is a weak comparison, for the territory bounded by the extracellular

waterways has never even been open to a committee of auditors who might like to chart its shoreline by boat.

But now, there are easily detectable substances permitting us to estimate the number of functioning and resting cells of a given kind in an organ or the whole body, to measure the state of their nourishment with blood, or to display, like a carpet, the total surface area of a cell receptor.

No less awesome is that giant scimitar -- the computerized axial tomographic machine. What earlier prophet could have imagined the harmless dissection of a whole body like a salami from head to toe -- or the opportunity to play the slices back and forth on a console, thus allowing estimations of the densities of unhealthy spots, the caliber of once-hidden canals, and the size and condition of the most elusive of glands.

I'm afraid you have relegated the traditional "Anatomy Lesson" to the wall of the small museum in The Hague where hangs Rembrandt's original. I visited last week the most recent of the new medical schools where the new students are beginning their debut in the profession through cadaver dissection. This touch of romanticism, a rite of passage, will help make them physicians, partly in ways that have more to do with philosophy than anatomy. I trust that anatomists and nuclear physicians are collaborating to supplement those ancient exercises with

forceps and scalpel with the new visions possible through tomography. To ignore this new perspective would be kin to teaching histology without reference to the electron microscope.

As for the diagnostic promise of the CAT scanners -- for each painful pneumoencephalogram or other risky procedure which this eliminates, there should be painted a small gold star on the fuselage of these giant machines. It is easy to condemn them for their cost; yet it is unconscionable to suggest that we can or should regress to the time when they were not available at all.

To you, nucleophiles from all over the world, I offer a salute for great ingenuity and special contributions to science, to medicine, and to health.

Now for the bad news.

Those areas of science like nuclear biology and medicine, within whose borders lie both discovery and exploitation of technical opportunity, are particularly vulnerable to important ethical dilemmas. The greater their capacity to produce change in a living thing or in a whole culture of people, the greater the injunction upon the inventors and users to do no harm.

I need not take your time on this occasion to discuss the avoidance of harm to persons, whether as normal subjects or as patients, who are the principal object of your investigations or use of your technology. The need to eliminate any unnecessary



exposure to radiation, ionizing or non-ionizing, had become an essential consideration in our society over the past several decades. It is a taboo which is frequently and necessarily reinforced by the constant examination of our environment and our world for potential sources of subtle damage to health and well-being. It is expressed in professional -- and societal -- demands for techniques of greater sensitivity, heightened quality of instrumentation, even more careful dosimetry and a meticulous recording of exposure to harmful nuclides or other sources of radiation. These matters, which are of paramount concern to you on a daily basis, I think we can set aside, as being ones you bear responsibly and need no further admonition from me.

There is a broader set of social issues that also involve that same injunction to do no harm. Here the dosimetry and calculation of risk and benefit are more difficult. The questions of morality are also complex and the responsibilities less clear. These are the matters related to unnecessary harm to the efficiency or usefulness even the economics of the "health systems" in which your talents and achievements are practically expressed. The dictum here must be: Promote no useless thing or unnecessary variation. Often nowadays, in moving through laboratories of nuclear medicine, one views a new marvel, capable of revealing statistical variations of body function to a new level of resolution. And one is sometimes constrained to ask, "Will this create more problems



than it will solve?" The exposure of finer grades of "abnormality" is even likely to create waves of anxiety in patients -- perhaps even more in their attending physicians. The perturbations sometimes reach points distant from the source, in hospitals or clinics, in accounting systems, and the tax structure and economy of a nation.

This is the stuff of which the important ethical dilemmas for science and society are made. Quite recently I talked to a science writer who said, "Do you think the problems between science and society are receding?" I replied that the ethical problems remain, larger than ever because science is ever more powerful, but both sides have begun to construct useful ways to cope with them.

From the side of science and of the medical professional, this has taken several forms. One is a recognition or admission of responsibility for frequent examination of the present realities and the prospects of technical inventions. A process of consensus must be in place which examines regularly and critically the state of the art and describes it in terms useful to the technically inexpert. Value judgments are essentially lay judgments which are the ultimate responsibility of the rest of society.

A crucial issue has been raised repeatedly in this half-century: How do you control technology? Some clearly would suppress the ability to explore the unknown. Others of us --

fortunately the majority, I think -- recognize that disciplining ourselves to choose what uses we shall make of discovery, is the only satisfactory way. In this latter, scientists and non-scientists have both sectarian roles and general responsibilities as citizens.

(Ad Lib Remarks on Secretary's Conference on Principles for Health Research, October 3-4, 1978.)

Perhaps my pausing to emphasize this general problem here places too severe an emphasis upon your own responsibilities. I do so, however, because the opportunities in your specialty are also disproportionately so great.

I vest my confidence in you as among the most likely to lead the movement of health technology in its already slated determination to go mainly in the direction of prevention. You must be in the vanguard of developing techniques to tell us the subtle differences in genetic constitution and nutritional status of individuals. You must apply your talents to the essential, sometimes desperate, race to order the physical and chemical forces in our man-made environment which threaten to overcome our powers of adaptation. You have to be eminently sensible and always humane.

I bid you welcome to Washington -- wish you much collegiality and intellectual renewal in your meeting this week. Above all, I assure you of the confidence that your biomedical peers have in you, and of the dependence society has upon you for continued inventiveness and for responsible adaptation of your discoveries.

REMARKS 1/

by

Donald S. Fredrickson, M.D. 2/

Thank you Mr. Turner. Ladies and Gentlemen.

This is a pleasant moment for me to join all of you in opening this parking area, the first completed portion in our modernization program of the Clinical Center and the addition of the much needed Ambulatory Care Research Facility.

Ground was first broken last year on May 31st, and today, nearly 16 months later, I am delighted to announce that we are able to add 900 more parking spaces for the convenience of all employees, as well as visitors to the NIH campus.

When the Clinical Center opened 25 years ago, little did we realize that our laboratory and patient care activities would grow so tremendously, and that our outpatient program would expand so rapidly.

Spring of 1982, for the completion of the whole structure, is still a few years away but to be able to see and use part of it today is tangible evidence that construction progress is being made.

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1/ Presented at the Ribbon Cutting Ceremony to open the first parking area of the Ambulatory Care Research Facility, NIH, on Monday, September 18, 1978

2/ Director, National Institutes of Health, Bethesda, Maryland

I am well aware of the tremendous activity, cooperation, and coordination that must exist in the creation of a large meaningful structure of concrete, steel, and glass. I am also aware that to create such a structure in the midst of our campus with a minimum of disruption and disorder adds an additional burden--especially when employee and visitor traffic must continue.

This burden is compounded when the construction is part of a busy research hospital with our primary concern for the patients within.

I have been pleased with the way all concerned have been so effective in making the construction as "painless" as possible.

To produce this Stage I Area, and the structure to be completed in the future, takes the combined efforts--and we like to feel, the best efforts--of many, names too numerous to mention in this brief ceremony but representative of the following:

- Architects and Joint Venture Designers
- The Turner Construction Company and Subcontractors
- The HEW Contracting, Architecture Engineering, and Construction people
- The General Services Administration and our own scientific and support personnel to include:
- Construction Engineering and Design Staff, Contracting and Security personnel.



To all, I say thank you. Let's keep up the good work.

To you, Mr. Turner, I say, I'm delighted to accept this facility from the Turner Construction Company on behalf of the National Institutes of Health, the Public Health Service, and the Department of Health, Education, and Welfare--as well as the staff and employees of NIH.

I also look forward eagerly to the completion of the Ambulatory Care Research Facility.

RECOMBINANT ODYSSEY II

A visit made by the

Director, NIH

September 24-30, 1978

Donald S. Fredrickson, M.D.

## Recombinant Odyssey II

### Introduction

This is not strictly a "recombinant" report; and if it were, it would not be the second of that genre. Since the composition of "Odyssey I" there have been numerous trips abroad which have involved a discussion of DNA Guidelines, viz., with Reichard (head of the Swedish "GMAG") in Stockholm in August, Huang and Ku in Peking in July, and the intelligences coming from a stream of European visitors to Bethesda like Byev from Moscow, Tooze and Kendrew from EMBO for the December 1977 hearings, etc.

These notes cover a relatively short trip to Rome and London (September 24-30, 1978). The Rome leg was fulfillment of a commitment made by Secretary Califano. He had earlier concluded a bilateral agreement with Italy involving the Ministry of Health and HEW. The arrangements for this appear not to have included adequate recognition of a pre-existing science exchange agreement concluded between Italy and the United States in 1967. NSF is the American principal in this agreement, but from the onset, NIH has funded the largest share of the biomedical research exchange. The Italian side is managed by the National Research Council or CNR (Consigli Nazionale della Recerchi). Dr. Quinn and I were off to Rome to reassure CNR that no injury to that older agreement was intended and also to encourage and strengthen the new ties to the Ministry of Health. The Rome visit was climaxed by a memorable evening at the American Embassy and comments upon it will conclude this report. Three days were also spent in London, where the heads of the European Medical Research Councils held their semiannual meeting. This included a trip to the MRC Clinical Research Centre in Northwick Park. A special feature of the London leg was dinner with the chairman and some members of the U.K. GMAG, which offered a unique opportunity for exchange of unofficial views between multiple members of this body and the NIH, the world's two principal sources of guidelines for regulating recombinant DNA technology.

### Recombination in Rome (Plasmid and Political)

Although there is a good bit of molecular biology in Italy, the use of recombinant DNA techniques is not heavy.

Prof. A. Falaschi is chairman of the Italian Committee on Recombinant DNA Research.\* This committee, which includes experts from CNR and from the

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\*The Italian Committee on Recombinant DNA is composed as follows: A. Falaschi, chairman; F. Blasi, University of Naples; M. Brunori, University of Rome; A. Carere, Istituto Superiore di Sanita, Rome; Clara Frontali, Istituto Superior di Sanita, Rome; N. Giammanco, University of Catania; M. Polsinelli, University of Florence; V. Sgaramella, CNR, Institute of Biochemical and Evolutionary Genetics, University of Pavia; P. L. Silvestri,

Istituto Superiore di Sanita, was set up by the Ministry of Health: (a) to review the present state of affairs in Italy and in other countries, and (b) to provide general guidelines for legislation on this matter. This committee held several meetings to consider various aspects of the problem and is now almost ready to present the final report to the Minister of Health.

In a meeting held by the Italian Society of Molecular Biologists in May 1977 there was the general consensus that research using recombinant DNA techniques should be encouraged with appropriate safeguards, including the training of the personnel involved; with this in mind a training project involving both CNR and industry (Montedison, S.p.A., Milan) has been initiated.

The equivalent of the "Health and Safety Executive" of Italy is located in the Superiore Istituto di Sanita (S.I.S.) (directed by Dr. Francesco Pocchiari). This "National Institute of Health," located in Rome, is not the equivalent of NIH. It has laboratories, scientists, and research, but it also is the FDA, EPA, and CDC of Italy, and does not have resources to support biomedical research extramurally, that being mainly the province of CNR, industry, and some private sources. Pocchiari has visited the United States, speaks good English, and is both affable and astute. No statutes or regulations have been promulgated in Italy to force adherence to guidelines for recombinant DNA research, and the S.I.S. does not carry out inspections of laboratories for this purpose.

Our affairs in Rome revolved about an axis running from Via Veneto (the American Embassy and adjacent Hotel Excelsior) to the CNR building on Pla. di. Scienza, the Foro Romano, and the Villa Taverna. Language is still a modest barrier to U.S.-Italian interchange, but as in some matters other than science the Italians do not need words for all conveyance of opinion or information. We had a valuable, fairly candid, and highly informative exchange with a great many people there.

Upon arrival at Fumicino Airport on September 25, we were met by Daniel Serwer, the Science Attache, and trundled in an Embassy car--with obvious installation of bullet-proof windows--to the Embassy for a few moments chat with Ambassador Richard Gardner. An economist-lawyer-professor at Columbia, the Ambassador speaks Italian and is refreshingly different from the archetypal political appointments heading some other American missions abroad. We had a brief exchange of greetings and compliments from Secretary to Ambassador and vice versa, and left the Embassy for antipasto, minestrone, and a briefing by Serwer and Danilo Bracchetti (a chemist from Orvieto) who has been at the Science desk in the Embassy for almost 20 years. The latter speaks excellent

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University of Rome; G. Tecce, University of Rome; G. Tocchini-Valentini, CNR, Institute of Cell Biology, Rome; C. Vetere, Ministry of Health, Rome; C. Sangiorgio, Ministry of Health, Rome, secretary.

The Italian National Research Council (CNR) is represented in the European Science Foundation Liaison Committee by Professor Arturo Falaschi, Director of the CNR Laboratory of Biochemical and Evolutionary Genetics, c/o Institute of Genetics, University of Pavia.



English and is a contact for all to remember when in Italy. Serwer commands what seems to be passable Italian and is a skillful, serious person who was very helpful.

At 4 p.m. we arrived at CNR and met briefly with Ernesto Quagliariello, Presidente of CNR. Quagliariello is a biochemist, trained by Britton Chance in Philadelphia; his principal scientific interests are in the field of oxidative phosphorylation. He is also Professor of Biochemistry and rector of the University in Bari, near Naples. His wife is a molecular biologist, working in the laboratory in Bari. Quagliariello is the quintessential Southern Italian, sentimental, grandiloquent, and with a mind that is not less creative if it be slightly less predictable than that of his northern counterparts. He was a protege of the recently murdered Aldo Moro (also from Bari). He is appointed to a job which seems to run five plus years. Marconi is the best known of his predecessors; they have also included Marshall Badaglio, who watched over Italian science during Mussolini's dictatorship. Quagliariello and I exchanged compliments, made somewhat tedious by translation, and reaffirmed the seriousness of the several bilateral agreements now binding us. The Presidente suggested in our first meeting that we should talk later about a special NIH-CNR "convention," but this did not re-enter our subsequent discussions.

Our group then joined a group identified as "the joint commission of CNR and the Ministry of Health," which appeared to have coalesced fairly recently and, one surmises, partially as a result of the HEW bilateral agreement.

Health science and politics are everywhere in a state of tension; the situation may be becoming particularly acute in Italy. Before the Parliament now are three major bills:

- The Health Reform Act. Already through one chamber, this bill is certain to pass this year. Should it not, the regions will be permitted to create their own separate health authorities. As Garibaldi learned earlier, unification of Italy is hard work and the Ministry of Health (MOH) will not let this chance for centralization slip by for lack of legislative initiative. This bill will create a National Council of Health with 72 representatives from the regions, one of whom will be a scientist. The MOH is authorized to create an advisory board which will issue an annual "health plan." This is to include research needs, a request which will be delivered to CNR. Thus some health science priorities will be pre-set, and CNR will have to respond to them (something in the way of an "Italian Rothschild Plan"). A national health service will also be established, a move which will open wider the lid of Pandora's box of regulatory and promotional needs designed to control the high cost of health.
- The Science Reform Act. This bill is a compromise worked out between the Communists and the Christian Democrats. It creates a Minister of Research (with portfolio) who will coordinate the

state budget(s) for support of science. This is viewed as favorable. The bill will also provide the politicians with control of CNR, which is viewed as potentially disastrous to science in Italy. The current committees of CNR, which like the Committee for Biology and Medicine (CBM) are now composed of scientists elected by the total community of practicing university scientists, will be abolished. Instead the CNR will be run by an administrative body of 12, half of whom will be political nominees, and most of the rest elected by all university professors. This committee will set up its own special advisory bodies to determine the distribution of resources to science.

- The University Reform Act. This proposal was not fully explained to us, but it would create a Ph.D. program (never extant in Italian universities) and change the method of appointment and perhaps tenure of faculty. Any change in university systems in most of Europe affects the workings of the medical and other scientific research councils, which support projects but not the costs of salaries for tenured researchers or other "indirect costs" as we know them.

The "Joint Commission," chaired by Professor Zannello, will attempt to "coordinate" some joint health-care projects, improve health services research, and in general, cope with the "societal" (meaning governmental and political) demands arising from attempts to rationalize a previously free and inchoate health system. The Ministry of Health has inadequate scientific expertise to cope with the problems facing it. Under our new agreement, the MOH will wish to contact agencies of HEW other than NIH for assistance or collaboration and we promised to assist them in any requests for establishing such contacts.

The end of the first evening we walked past the Foro Romano (which due to the wear and tear of tourist hordes is no longer open or glorified by Son et Lumiere in the evenings) to the Hotel Forum. There the CNR laid a pleasant dinner for us on the roof. The prosciutto melone was followed by tortellini alla forum, small, succulent round pastas which Pocchiari informed me, sotto voce, were invented in Bologna and "modeled" after the navel of Lucrezia Borgia. Scallopine al fundador followed and we ended with a dessert a scelta. Because we were all now fortified by ample pinot bianco and corvo rossa, Presidente Quagliarierro was moved to deliver an extended toast covering, in addition to our collaboration, Lucrezia Borgia, the tabula rasa, etc. In the interests of time, the President's remarks were left unsullied by translation. I responded as simply and unsentimentally as one can, while contemplating the Foro Romano, and the silhouettes of the pines above the Villa Borghese moving in the gentle breeze cooling the Roman night.

On the 26th, we met the executive committee (5 members) of the Committee on Biology and Medicine (CBM), a group which dispenses about 1/12th of the CNR budget. This overall budget, incidentally, has steadily increased over the last 5 years at a rate exceeding inflation. The CBM is composed of 22



scientists elected by their scientific peers (the biomedical ones, I believe) in the universities, plus 2 members elected by the first 22 and one appointed the president of CNR. The "president" or chairperson of the CBM is elected by that body. Terms are for four years and may be renewed once.

The tasks of the CBM are as follows:

- (1) To give advice and views to the president of CNR and to be the council of presidents (one member each from the 11 CNR committees).
- (2) To operate scientific centers of CNR. CBM has 34 of these; 8 are "outside" universities, the rest are within. Their total staff includes 400 professionals.
- (3) To make grants, mainly to universities. Last year it had about 1,300 applications and awarded about half. The number of "good, unfunded" applications helps them compete for CMB share of annual CNR budget.
- (4) To control a few targeted programs. These 5-7 year programs take about 8-10 percent of the budget and presently include 7 topics, among which are: medical technology, reproductive biology, virology, preventive medicine, and cancer therapy (these are not identifiable with the collaborative areas selected under the joint HEW-MOH agreement).
- (5) To award long-term or short-term fellowships.
- (6) To support meetings, publications, etc.

The CBM has in the past several years been under the direction of Dr. Luigi Rossi Bernardi, an M.D. later trained as a biochemist by Rowten at Cambridge. He speaks good English and is at the Istituto di Agraria, University of Milano. He described recent Italian efforts to improve the system of awarding grants according to scientific excellence. Last year applicants were divided into classes. Group A included the known producers, i.e., those possessing a bibliography; Group B included those without previous papers. The money goes to subsections according to the number of A's among the applicants. The division is largely by a formula that amounts to about \$10,000 per grant. Per capita comparisons between the U.S. and other countries are hazardous because of the multiple sources of university funding for costs of research in European countries. Awards are made only for one year, but can be renewed. No progress reports seem to be filed and heretofore the decisions have been solely ad hominem. From comments by Professor Giovanni Magni, of the Istituto di Genetica in Milan and also of the executive committee, the granting process is still too political in nature; and one service the Italians would greatly desire through their collaborative agreements with the U.S. would be some kind of review of Italian scientists. They would expect this partly to come from

U.S. choice of collaboration, but Magni also indicated that direct review by our much larger and experienced peer review process would be a great boon to them. We indicated how difficult, indeed impossible, this would be, even when collaborative programs are in progress. Italy, like all countries in Europe, has great difficulties assembling a critical mass of expertise for review of scientific proposals in the fashion of NIH.

Later this day we met again with Presidente Quagliarierro, Dr. Bosco, a representative of the Ministry of Education, Dr. Cimino of the Ministry of Health (which is headed by Signora Anselmo), Dr. Pietromacchi from the Foreign Ministry, Professor Brancatti for the Minister of Research--presently without portfolio, Dr. Pocchiari, Director of the Institute of Health, the head of the CBM target programs, and several others. This highly formal meeting, with translated segments, was a further exchange of ministerial greetings, compliments, reiteration of hopes for collaboration, etc. For our part, we indicated a belief that collaboration began by understanding between participants of what were the real and common interests of the participants, where lay the special talents, and how could scientist-to-scientist contacts be enhanced. We promised to do our best to continue the old CNR-NSF relationship and to help the newer HEW-MOH agreement flourish, by both combined and separate efforts. I encouraged the CNR president to come personally to negotiations on the CNR-NSF treaty to take place in Washington in January 1979, and indicated how pleased we would be if he could visit NIH in the process.

### Public Speaking

At 6 p.m. on the 26th I was scheduled to give an "informal public lecture." By 6:15 the public was not large and the Baronessa Reggio, one of our translators, comforted me with the observation that in her native Venice (La Serenissima of the "other Italy")--6 p.m. meant 6, but in Rome or northward 6 means 7, or later. Somewhat later a fairly sizable crowd collected, including a couple of NIH grantees, a number of other scientists, including surprisingly Ernst Chain's wife (Ernst, a Nobel, has labs at the S.I.S.), and several who seemed to be members of the press. I began by expressing pleasure at the opportunity to give earlier lectures in Italy and confessing that there was a "Sala di Riunione" in my name at the Ospedale Maggiore in Milan. Once, on receiving the "Modannina Prize" in Milan, I lectured in a room where Mozart had played. The CNR Aula Major, finished in 1936, during the middle Mussolini period and covered with murals showing earlier Italians in heroic dimensions, clearly would not claim this degree of distinction, but I conceded that it, too, must harbor distinguished ghosts from Italy's extraordinary past. Foreshortened by consecutive translation, my extemporaneous remarks summarized the immediate future of science, including its substance (borrowing heavily from the lectures of Weisskopf, Calvin, and Crick at last week's Schenectady symposium) and its societal interfaces as dealt with earlier in "The Public Governance of Science" (the Columbia Lecture in 1976) and the Nobel Symposium Lecture in August 1978.

At the end, Presidente Quagliarierro closed with a brief peroration and generously presented me with a four volume archeological treatise, "the last



copy in the house" of Festos e la Civilita Minoica, by Doro Levi, a project funded by CNR. A man rushed up to ask, "Did you say the scientists must decide what research should be done?" "Yes, they must make the first determination, then others can put their values on the decisions, if they are paying for the research." This question is soon going to be asked more and more in Italy. A number of the audience, especially younger ones, seemed ready for further debate on the issues raised, but regrettably, we had to rush to the Embassy for dinner.

### Recombination in London (GMAG)

On the 27th we arrived in London. At 5 p.m. we had tea with Jim Gowans, head of MRC, in his office at Park Crescent, and talked about special problems of the MRC--Rothschild not working well, redundancy clauses beginning to complicate the decisions not to fund further less productive and untenured scientists in MRC units ("once a grant, always an employee"?)--and general issues common to support of health science everywhere.

At 6 p.m. we moved a few blocks to Ciba House, where Gordon Wolstenholme, the retiring director of Ciba Foundation and retiring chairman of GMAG, had assembled at my request an assortment of his GMAG colleagues for a drink and dinner with us. The attendees, in addition to Joe Quinn and myself, were: Professor K. R. Dumbell, R. J. C. Harris, Professor M. H. Richmond, Professor R. Williamson, J. A. Gilby, Dr. D. O. Haines, and Dr. J. H. Morris.

These include 7 of the 24 members of GMAG (see Appendix A for full listing) and John Morris of MRC, who is the Secretary. Of the members, Dumbell, the virologist at St. Mary's, arrived with most of his hair shorn off; he has been taking multiple showers daily as a member of the official team investigating the recent death from smallpox of the science photographer in Birmingham. The victim's laboratory, we learn, was a floor above the repository of the virus, 60 yards lateral to it, and in the opposite direction of the air currents. It seems that monkeys housed in another laboratory there are suspected of being an alternate source of virus (one hopes not, for the head of the smallpox unit has died of self-immolation after this tragic infection). Harris is the Director of the Porton Laboratories and indicated that Walter Gilbert of Harvard had been working in his P3/P4 facility (confirming what Jim Watson had told me a week earlier), and that Stan Cohen had made a tentative booking in case our guideline revisions weren't issued here. The decampment of scientists to locations with less restrictive guidelines has actually been less than one would have predicted. (There are now two P4's in Europe, one at Porton and another opened in Paris a week ago, according to Burg of INSERM, whom we saw the next day.) Harris also confirmed that the P4 at Heidelberg wasn't yet working; he also noted that this EMBO facility was encountering some town-gown antipathy there.

Richmond, Professor of Bacteriology at Bristol, was the person most concerned and critical of the containment changes in our revisions. He felt that the amount of new information at Ascot was not great, that Falmouth also had heard little new, in support of the decrease in containment. I agreed about Ascot, but felt that Falmouth had considered significant new information, including

the latest Curtiss findings. The key element, however, in both places was calm and complete reconsideration of what had been known before. I reminded him that there were no data earlier to support the containment levels NIH and U.K. had set initially. He did not deny this and we did not discuss containment reduction further as a specific topic, except that several members indicated GMAG was "considering" revisions of the Williams report. It would, they said, be "sent around for general comment," possibly a reluctant imitation of their American cousins' endless rounds of public consultation. The members were a bit annoyed when I described our November meeting of I.R.B.'s--"We are always a few weeks behind," exclaimed Williamson, "We'd planned to do that, too." He is a scientist and representative of the Science, Technology, and Managerial Staff union, and a young, earnest, and attractive person. On GMAG he clearly is a frequent sparring partner of Gilby, Beecham's Technical Director and the member representing the Confederation of British Industry.

I explained in some detail: (1) how I expected our proposed technical changes to stand after the September 15 hearing and how our procedural matters might be further revised; and (2) why I no longer supported a law in the U.S.--because it seemed impossible to get the desired universality without great excess and unnecessary complications, such as the medieval features of the first bills, Kennedy's commissions, and Dingle's NEPA foolishness added in the conference report of Rogers' last bill--England now has a clear legal requirement that everyone register with both GMAG and the Health and Safety Executive. This makes it the only country in the world with such legal restraints on the private sector and everyone was a little uneasy about that.

We talked about I.R.B.'s. Industry, like Beecham's, has no outside (public) members on its committees. GMAG consideration of industrial proposals is still awkward; some of the union representatives are "walking out" rather than participating in the review of them.

Dr. D. O. Haines is one of the Health and Safety Executive leaders, who is an "Assessor" or ex officio member. He affirmed a GMAG/HSE intent also to give local committees more authority.

One thought suggested by Williamson was that if we require recipients to whom recombinant H's or V's are shipped to give us an MUA (Memorandum of Understanding and Agreement), our scientists should reciprocate and file MUA's with GMAG. Britain presently has no way to cope with the commercial products of recombinant DNA technology, the release-into-the-environment issues, or some of the other issues covered by our Guidelines or which our regulatory agencies are confident they cover in their authorities.

Our dinner, in an upper floor dining room at Ciba House, ended with what English authors are fond of calling "a most excellent port." I observed to Wolstenholme that one major difference between GMAG and the U.S. RAC was the vastly superior quality of food available to the former. GMAG will now have to find other social quarters, they having been donated by the now retiring chairman. His replacement, indeed even GMAG itself, is subject to a possible



new change in British government. One is struck by how popular is Shirley Williams, the present Minister of Education and Science in Britain. This is a far cry from Barbara Castle, her predecessor, who was not hesitant to create an Institute for the Deaf when back-benchers found they could not hear her.

### Recombination Elsewhere

Recombinant news from the rest of Europe trickled in the next day at the EMRC meeting. Ms. Zobrist from ESF indicated that their assembly was watching the U.S. revisions closely and was considering similar downgrading. Many were loathe to move, however, until the U.K. overcomes its reluctance. Save for the British rule, no laws have been enacted in any European country. Halter, the Belgian, who tends to view events dramatically, stated that the EEC directive designed to have a single "statutory" call for adherence to guidelines was "moving hard." Representatives from other countries were less sure and there was sentiment to the effect that, because a law in the U.S. was now stalled, others would see that EEC did not move precipitously to enact one. The Swiss, not in EEC, clearly are not for a law there. Some new information on DNA activities in Denmark is included in Appendix C.

### European Medical Research Councils (EMRC)

The semiannual meeting of the EMRC was held in the Royal Society on September 28-29. In a smallish room containing portraits of some of the less famous Presidents of the Royal Society, the attendees (Appendix B) discussed numerous items of which three aroused the most interest.

1) Its own identity crisis. As a "standing committee" of ESF, the EMRC now submits an annual report which it suspects no one reads. One group, including the Dutch and Swiss, wish EMRC to identify itself more vigorously as a part of ESF. Another wing, a minority led by the British, want to return to the good old days of informal club-exchange of views and experiences. The discussion, I think correctly, led to a consensus that ESF will get its own biomedical group if EMRC withdraws, and it's better for EMRC to remain in ESF and control its biomedical interests than to seek peaceful repose in isolation. (This all is somewhat reminiscent of the NAS-IOM "struggles" in the U.S.) Biology and its medical applications are the most intoxicating offering of science today and can not be separated from all the life sciences. I was also impressed by a phenomenon I will call Eurospeak--the effective manner in which all these countries have learned to exchange views on difficult matters with delicacy and calm. The national groups are subject to stereotype regardless of their individual representatives, but the ecumenical effort is impressive. One is struck by the role of the Danes and the importance of the small but audible instrument they play in the European orchestra. (It was they who catalyzed formulation of EMRC in 1971, through the particular efforts of Ms. Korning who now lies critically ill in Copenhagen and could not attend this meeting.) Not terribly suave, but thoroughly credible, the Danes--conditioned to survive on a flat and vulnerable peninsula between so many giants of different temperament and ambition--are

sources of harmony and leadership so subtly applied that each of the larger powers will emerge with the impression that it is it which has magnanimously saved the situation. It is also noteworthy how the American guest, the rich giant NIH, the only observer allowed into Europe's biomedical salon, also can play a powerful role here, provided its guest performances are muted and dotted with occasional passages of virtuosity.

2) Technology transfer--an example, perhaps, of the last observation above...this jargon-laden topic fell largely to the U.S. to discuss. Our description of "technical consensus" was met with great interest and started numerous small fires in the dry tinder of an MRC-land parched for credibility and relevance as the political dragons move recklessly about, breathing hotly for practical solutions to the endless problems of health systems. Burg, given to Gallic excess, proclaims the NIH exercises a salvation of embattled science; the Italians--who have so recently heard me before--do not contest; the Swiss sense the pragmatic beauty of accommodation without surrender; the Germans will think it over; the Finn--socialist Heikkinen--contests it, for "all science must prove that it works for the people." Nevertheless, we are requested to provide "more discussion of this in the U.S.A. in April 1979, please . . ."

3) Rothschild is failing. No single item seems so obvious and troublesome as the dissatisfaction with health services research in every EMRC country. The new British chief scientist of the Department of Health and Social Security, Dr. A. J. Buller, ERD, asks to visit us soon, seeking any ideas as to how Health and MRC can use the 20 percent set aside for Health. Presently it is identifying MRC projects it wishes "to sponsor," rather than initiating its own (it already has other contract funds for this purpose). The fear is that a parliamentary inquiry could result in loss of the MRC funds now "set aside" for health research.

The British hosts entertained us well. The dinner on September 28 at the Dorchester Hotel was addressed by Sir James Hamilton, KCB, MBE, the Permanent Secretary, Department of Education and Science, and ended with "an excellent port." The evening of September 29 was spent in a boat on the Thames, where the guests included Lord and Lady Shepard, Chairman of the MRC Board, a flute, clavier and soprano, and a lot of excellent port.

#### Visit to MRC Clinical Research Centre

We visited this facility on the afternoon of the 29th. (See Appendix D for description.) The Director, Christopher Booth, was present and we met some of the scientists and heard presentations of both clinical and laboratory research.

#### Finale (Dinner at Villa Taverna)

Ardent readers of this series will recall that the first report ended at the American Embassy in Helsinki where about 20 eminent Finnish scientists of many disciplines, the Director of NIH, and Ambassador Mark Evans mused upon



the matter of allowing the public to discuss and direct the future of "genetic engineering." Since Joe Quinn was also there, I assume that he had something to do with creating a similar happening in Rome on the night of September 26.

As guest of honor at a dinner given by Ambassador and Mrs. Gardner, I found my Helsinki role repeated with more southerly intensity and special overtones. Villa Taverna, a beautiful estate behind the Villa Borghese, includes an old, spacious house with elegant gardens, surely one of the most beautiful of American embassies anywhere. We were fortunate to have not only Italian-speaking Sr. and Sga. Ambassadors, but another interpreter, Ms. Anna Larson, who sat at my side after dinner to provide fluent and rapid translations. Her interpretation of my toast, in response to those of Ambassador Gardner and Ernesto Quagliarierro, was so good we drew applause.

As we gathered for coffee and brandy in a spacious room of the Embassy after dinner, the Ambassador indicated we were to touch upon several topics which he would introduce and I would first comment upon. He asked three questions:

- (1) How do politics affect biomedical research in the U.S.?
- (2) Have recombinant DNA or survival technologies created special problems there?
- (3) How do members of the public affect science policy and practice in the U.S.?

I suspect that I gave too vivid a description of how Congress determined support of biomedical research in the U.S. Certainly I should not have said it entered into the transactions "more than any other parliamentary body, including the Presidium or central Committee in the U.S.S.R." While this is unquestionably true, it is too much for scientists in a country threatened with a Communist government in Europe to digest. It also leads to confusion between political interactions with and the "politicization" of science. Quagliarierro was upset by these images. Others indicated that there is no dialogue possible with Italian politicians. There may be several reasons for this. One is that the scientists have not cultivated the necessary contacts or learned to understand their societal responsibilities. Another may be the character and quality of Italian deputies, perceived as too agrarian or rustic or as hacks, lacking in capacities necessary to understand the complexities of science. The Science and University Reform Acts, already mentioned, became the subject of acrimonious debate between the Italian guests (Appendix E). Counsellor Vaiano defended the necessity of political direction of science. Prof. Giovanni Magni allowed that he was already known as an "infante terribile" and therefore would not hesitate to characterize the potential changes in the science acts as a potential disaster for Italy. Giorgio Tecce, a somewhat more "political" scientist, said as much, but with greater circumlocution. The Ambassador grew somewhat concerned as to how and when this was all going to end when midnight arrived. With grace he heard out the last deposition.

Italy has a totally literate population, which consumes 100,000 copies of the Italian version of Scientific American. But the public, for its "confrontation with science," depends on the legislature. So it will be with most countries. When the latter is beyond its depth in understanding the scientific process, or cannot effectively be approached by the scientists and academicians, the danger is grave, indeed. I admire the Italian scientists. I do not envy them. If serious political folly supervenes, they doubtless will survive in some way, sustained by Tortellini, and guided by the reflexes for political accommodation developed over centuries spent in the midst of one of the most productive and intensive cultures in the world.

# GMAG

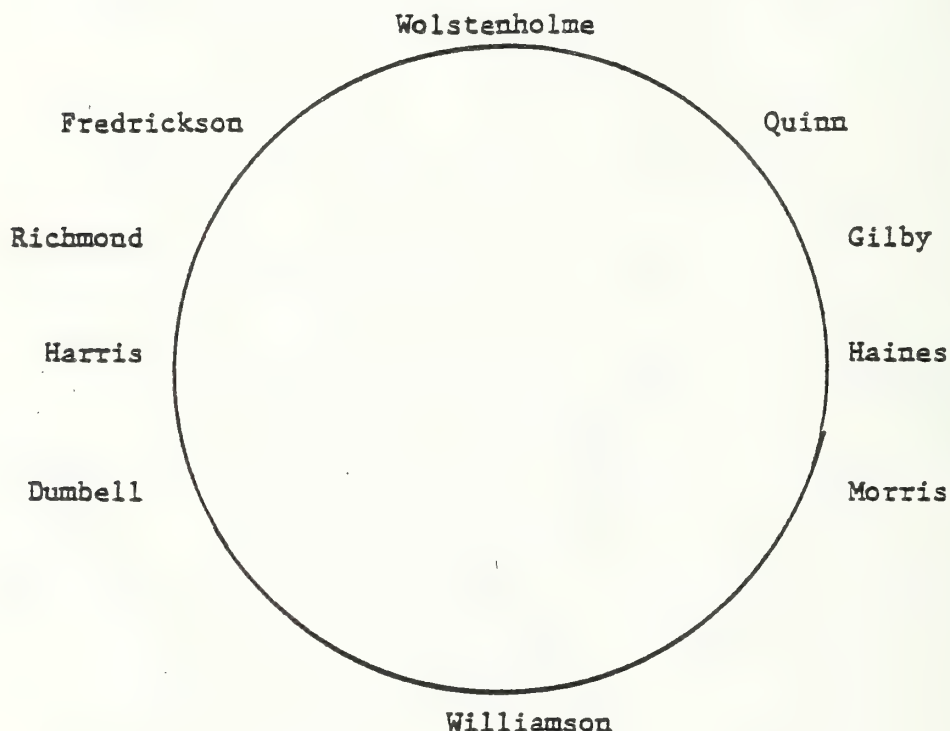
Genetic Manipulation Advisory Group  
at Medical Research Council  
20 Park Crescent, London W1N 4AL  
telephone 01-636 5422

reference:

Dr Fredrickson

DINNER WITH GMAG MEMBERS 27.9.78

At the dinner given by Sir Gordon Wolstenholme at the CIBA Foundation you met eight members of GMAG, as indicated on the following table plan:



The full titles and affiliations of the above, and the names of other members not present, are indicated in the attached list.

Please let me know if you would welcome further details.

John Morris  
Secretary, GMAG

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DENMARK

## DANISH MEDICAL RESEARCH COUNCIL

Recombinant DNA Research

In October 1977 the Registration Committee for Genetic Engineering, set up by the Research Councils, submitted the enclosed report containing a proposal for a regulation of this research area in Denmark. The Research Committee of the Parliament has discussed the content of the report, and it has been submitted to the involved Ministries and organizations. The results of the hearing are expected to be available at the end of 1978, and then the appointment of a permanent supervising commission for genetic engineering research will be taken under consideration. Furthermore, it will be considered whether a separate legislation concerning this area is necessary.

From the EEC a draft of a directive has been issued, and this directive could, if occasion should arise, form a sufficient legal regulation of this area also in Denmark.

For the time being the Research Councils' Registration Committee continues its work, and the Committee has registered 5 genetic engineering experiments, all included in the category involving only small risks in accordance with the guidelines of NIH. The experiments are carried out at the University of Aarhus and the Carlsberg Research Laboratories. Moreover a collaboration in this research area has been initiated between Danish industrial companies and the universities in Aarhus, Odense and Copenhagen.

Council for Medical Research, NAVF, Norway.

REPORT ON RECOMBINANT DNA RESEARCH.

NAVF's Committee for Recombinant DNA Research was appointed in 1976 to:

- follow international developments in this section and to keep NAVF informed, also on the ethical aspects of this research and on necessary measures for containment,
- find out the probable scope of DNA research in Norway in the future.

On the basis of a study carried out in 1977, the committee has concluded that very little such research involving any degree of risk is done in Norway at present and there is no reason to believe that activity in this field will be intensified in 1978. The committee has discussed regulations to control this type of research, and in this connection has contacted the Directorate of Labour Inspection and the Department for Research at the Ministry of Education.

One of the committee members represents NAVF on the ESF (European Science Foundation) Committee for DNA Research. Early in 1978 the Ministry of Church and Education requested the committee to make a professional report on the risks entailed in this research in Norway, evaluate the necessity for regulation and control, and make a survey of the scientific, economic and administrative consequences of such control.

A draft report has now been prepared.

It is very improbable that any research of this type, other than pure basic research, will be carried out in Norway in the foreseeable future. It is also improbable that research at high risk levels will be carried out in this country. But it is important even so that regulations are imposed as soon as possible.

The committee has recommended that for the present the guidelines approved by N.I.H. apply in Norway.

## MEDICAL RESEARCH COUNCIL

Clinical Research Centre

From time to time during the Council's history, the idea has been mooted of a special 'research hospital', to provide a clinical counterpart to the Council's first and largest in-house research establishment, the National Institute for Medical Research at Mill Hill. The idea of combining such a research institute with a district hospital was taken up in 1961 when the building of a new hospital at Northwick Park, Harrow, provided the opportunity to plan the new research institute and the hospital together. The Clinical Research Centre, along with Northwick Park Hospital, was formally opened in 1970.

The first Director of the Clinical Research Centre was Professor J. R. Squire. Professor Squire died in 1966 before completion of the buildings, and was succeeded by Sir Graham Bull. Dr. C. C. Booth has been Director since April of this year when Sir Graham retired.

The setting up of a research centre in conjunction with a district hospital has many advantages. On the one hand patients in the locality have the benefits of the latest advances in medical science and immediate access to the special facilities for diagnosis and treatment that are available in the research centre; on the other hand, research workers are brought into direct contact with the everyday problems of medicine. This association between medical research and the care of patients may be seen in the design of the buildings and in the arrangements for the staffing and operation of the complex. Many staff of the research centre carry responsibility for routine patient care, whilst research facilities are available to those of the hospital staff who wish to pursue a research project.

The Centre brings together in one place a wide range of skills, not only in the various branches of medicine, but also in related basic sciences. At present it is organised into the following scientific Divisions:

Anaesthesia	Hospital Infection
Bioengineering	Immunochemical Genetics
Cell Pathology	Immunology
Clinical Chemistry	Inherited Metabolic Diseases
Clinical Investigation	Medical Computing
Communicable Diseases	Perinatal Medicine
(including the Common Cold Unit)	Psychiatry
Comparative Medicine	Radioisotopes
Computing & Statistics	Radiology
Electron Microscopy	Rheumatology
Haematology	Surgical Sciences (including Transplantation Biology)

The Centre has about 200 beds: two- and four-bedded wards are situated close to the clinical research laboratories and the special facilities for metabolic studies. In addition, there are over 600 beds in the hospital itself.

## DINNER AT VILLA TAVERNA IN HONOR OF DR. FREDRICKSON

TUESDAY, SEPTEMBER 26, 1978 - 8:30 P.M.

AMBASSADOR AND MRS. RICHARD N. GARDNER

Dr. Donald S. Fredrickson, Director, National Institutes of Health

Dr. Joseph R. Quinn, Fogarty International Center, National Institutes of Health

Professor Ernesto Quagliariello, President, CNR

Counsellor Paolo Vaiano, Chief of Cabinet, Ministry of Health

Professor Giulio Tarro, Ospedale Cotugno, Universita' di Napoli

Professor Luigi Rossi Bernardi, Istituto di Agraria, University of Milano  
(biochemist)Professor Giorgio Tecce, Facolta' di Scienze, University of Rome (oncologist/  
geneticist)

Professor Giovanni Magni, Istituto di Genetica, Milano (genetics)

Professor Lucio Luzzatto, Direttore, Istituto Internazionale di Genetica e  
Biofisica, Napoli

Dr. Salvatore Aloj, Istituto di Patologia Generale, Napoli (NIH grantee)

Professor Enrico Calef

Professor Fabrizio Monaco, Policlinico Umberto I. (NIH grantee)

Professor Leonardo Santi, Direttore, Istituto di Oncologia, Universita' di  
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Dr. Maria Antonietta Manca, Italo-American Medical Institute

Professor Alfredo Leonardi, Istituto Mario Negri, Milano

Mr. Michael Calingaert (Minister)

Mr. Daniel P. Serwer (Science Attache)

Mr. Danilo Bracchetti (chemist, Science Attache staff)

Miss Anna Larsen (interpreter)



# National Conference on Health Research Principles

October 3 and 4, 1978

## Conference Report

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE  
Public Health Service                      National Institutes of Health

Editorial note: Also published in Clinical Research 27: 98-100, 1979.

REPORT ON THE NATIONAL CONFERENCE  
ON HEALTH RESEARCH PRINCIPLES

Department of Health, Education, and Welfare

TABLE OF CONTENTS

	<u>Page</u>
I. <u>Conference Chairman's Overview Statement . . . . .</u>	1 ✓
II. Revised Draft DHEW Health Research Principles . . . . .	7
III. Analysis of Draft DHEW Health Research Principles Presented at the National Conference . . . . .	23
A. Fundamental Research . . . . .	25
B. Clinical Applications and Health Services Research . . . . .	30
C. Health Regulation and Promotion . . . . .	36
D. Research Capability . . . . .	41
E. Unifying Concepts . . . . .	47
IV. Conference Panel Reports . . . . .	53
A. Fundamental Research . . . . .	55
B. Clinical Applications and Health Services Research . . . . .	65
C. Health Regulation and Promotion . . . . .	73
D. Research Capability . . . . .	81
E. Unifying Concepts . . . . .	95
APPENDIX A: Draft DHEW Health Research Principles Presented at the National Conference . . . . .	107
APPENDIX B: Roster of Panel Membership . . . . .	137

### CONFERENCE CHAIRMAN'S OVERVIEW STATEMENT

On October 3-4, 1978, DHEW Secretary Joseph A. Califano, Jr., convened a National Conference on Health Research Principles. At this Conference, five Panels--selected by the Secretary from nominees of all of the DHEW health agencies--heard testimony from many public witnesses concerning a draft set of principles developed by the agencies. At the close of the Conference, the Panels presented preliminary reports. These were edited by the Panel Chairmen, given to all Panel members for comment, and in some cases revised before submission as the conclusions of the Panels. The Conference staff then analyzed these final reports and prepared a revised set of draft principles based upon the Panels' recommendations. All of the above documents accompany this statement.

In accordance with the Secretary's policy of seeking public advice throughout this process, these documents are being presented now for evaluation by the Institute of Medicine and for public review. As this next phase of comment and revision proceeds, however, the DHEW agencies need not delay their consideration of the preliminary results of the process initiated by the Secretary last May. The present DHEW support and conduct of health research merit review in light of a number of the major conclusions of the Conference.

Health research in the United States has reached a stage of highly complex organization, fairly remarkable achievement, and heavy dependency upon government support--all in the space of a few decades. The promise of the enterprise still far exceeds its failings; and some perceptions of the latter are misconceptions of what science ought to be able to do and cannot do (at least now). Most of us number ourselves among the strong supporters of health research, but our reasons are highly diverse. Thus, any distillation of the essence of health research--the important principles upon which its public support and conduct should rest--must yield a diverse mixture. And such was the product of the Secretary's Conference. There was, however, one important control in the process not present in all similar deliberations. All participants had a common reference to consult, from which they could select certain qualities to be preserved or rejected, and from which they could also choose among initiatives to be encouraged; and finally they were allowed to add such principles as consensus seemed to permit. The resulting new fabric was to be rewoven on the warp of the original draft.

The revised principles are subjective and uneven. They are in need of further refinement, reordering, and transmutation to goals--the next phase in the process which the Secretary announced should be completed by next spring. The principles are, however, a more thoughtful and

valuable beginning than many observers expected. They reflect angst of different kinds: that fundamental research not be sacrificed to expediency, that access to scientific help not be denied to any of the health missions, that an essential pluralism of health sciences not be stifled by monolithic creations, or that budget displacements not substitute for skillful management rearrangements designed to assure effective interaction and collective responsibility among the health agencies. Some of the Panels were reluctant to accept as a given the concept of austerity--the requirement that any change be met through fiscal redeployment. However, this reluctance was accompanied by reasoned arguments on what alternative sources the commentator would use.

The Conference reports provide a litmus to test the status of certain concepts and definitions. The term "basic research" seems to have become too ambiguous to bear its important burdens. "Fundamental" is used in the reports and clearly implies research that is either laboratory- or clinic-based, aimed at mechanism, and not yet targeted toward specific, practical application in health care. The "Science Base" term now being tested by NIH in allocation definitions appears throughout the reports because it covers not only fundamental research but certain resources essential to that enterprise. Another area of much concern, health services research, was deliberately given a limiting definition of "scientific inquiry into problems associated with the actual organization, financing and delivery of health care services." Categorical clinical investigations, sometimes grouped with health services research, were advisedly aggregated under "applications" research, a category including multiple kinds of developmental research of importance to numerous agencies. The NIH is now using Applications Research as a second major allocations category. The third is Technology Transfer, a useful description for a research agency to define its activities closely complementing the service, health promotion, or regulatory missions of some sister agencies. The fourth category is Training or Manpower Development.

The SATT system --Science Base, Applications Research, Technology Transfer, and Training--could be adapted to analyze all DHEW health research or science activities. The importance of some such rationalization lies in recognition of strong recommendations that emerge from the Conference reports and revised principles calling for different ways to carry out the distribution of resources among these different categories. Thus it is suggested that the processes of selecting and financing "science base" and "applications" activities, whether within one agency such as NIH or across agencies, should rest on different principles, with needed funds perhaps coming from different purses.



The conferees offered concrete suggestions while reaffirming the essential Federal contribution to building the "science base." All five of the Panel reports contain suggestions for protecting and improving the knowledge-development capabilities that facilitate the health and survival of man and his world. Consideration of these proposals by both the Administration and the Congress is merited. They include potentially useful components of a multi-year budget strategy. The most frequent assertion of commentators was that DHEW support of the science base should be stabilized to the extent possible during the period covered by the multi-year strategy. As the Secretary noted in his address before the Annual Meeting of the American Federation for Clinical Research in April and reinforced at the Conference, the building of our current capacity of knowledge development represents a 25-year investment of the American people, and to jeopardize this investment so carefully assembled over the years would not be in the public interest.

The Panel reports also suggested budgetary and organizational changes. Some of these address areas where reorganization is under consideration with DHEW. On the important issue of creating knowledge to meet the needs of regulators, the Panels, while not endorsing the concept of "mission-oriented fundamental research," did nevertheless support the need for effective capability in each agency to conduct research aimed at its immediate needs. The National Toxicology Program, recently formed to unite research and regulatory agencies along a common front, was not known to many of the conferees. In some aspects, it goes beyond any design proposed at the Conference.

A bold suggestion was made for establishment of a type of health research council at the Secretarial level to unite the agencies for collaborative efforts in applications and health services research. This is a level and degree of interaction greater than now exists. Two fairly radical suggestions were made in relation to this proposal. One was that health services research be conducted by an agency under the joint stewardship of such a council. Another was that a special (Secretarial) research fund be established from which searches for urgently needed new knowledge be funded. How such a fund might be administered, or how the Congress might view much of the proposal, is left to be considered. The structured interaction among all agencies that was proposed as a means to enhance the development and application of knowledge to all health missions deserves careful thought; many believe something like this is overdue. Creation of an appropriate mechanism for this purpose might be one of the minimum goals arising from this search for principles.

The conferees did express the view that if present strengths are to be maintained and enhanced, new organizational arrangements should occur around unmet health needs of mutual concern. This is the preferred alternative to broadening the research missions to embrace regulatory or care functions, or expanding the latter to include major research activity. Tomorrow's opportunities for improved health depend on research advances today, but such advances can only be impeded by a confusion of research and service. The ultimate goals of both are the same, but the short-term purposes, settings, skills, disciplines, and processes involved are not. More systematic ways of meeting regulation and health care needs could involve the resources of both the research agencies and the service and regulatory agencies, yet would not compromise the basic functions of either.

These highlights of the Panels' conclusions indicate that a useful process has been started. Whether the promise will be realized depends upon our continued efforts within DHEW, as they are also guided by the further contributions of many outside the Department who have compelling interests in the biomedical, behavioral, and social science components of health research.

## CLOSING REMARKS\*

by

Donald S. Fredrickson, M.D.\*\*

Historians may or may not note that on these two days we all met in Bethesda. At the Secretary's bidding, we sought to assemble a fabric of health research principles. Perforce we have had to do this in pieces. When it is revealed to us in the next few moments it will not be of uniform color or texture like the gold-cloth of Rumpelstiltskin.

It will be motley, patches of different color and shape. The yarn will vary, too. Some of it will be of a kind much used and well-known in this region for work designated as "creating-the-record." It derives its widely variant texture from its adversarial nature, the stuff of somewhat parochial interests. Yet it adds variety and sometimes surprising strength to a final material.

Much of the weave also will come from broader views, yet themselves always bounded at the extremes by specialized experience, training, and purposes. Committees cannot easily construct horses or principles.

No one expects Olympian perfection or even completeness

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\* At the National Conference on Health Research Principles held in Bethesda, Maryland, at the National Institutes of Health on October 3-4, 1978.

\*\* Director, National Institutes of Health, Bethesda, Maryland.

in the product carried here, still disassemble, by the persons on this stage.

Still--and deliberately without prior knowledge of what the next few minutes will reveal--I want to pronounce this exercise as a successful one.

Successful:

- in harnessing some of our country's great talent and prodigious energies to the tasks set by a fairly ruthless agenda.
- in revealing the good sense and reason demonstrated by so many people who have at least one common interest and yet see it in such endlessly different perspectives.
- in gaining your particular contributions . . . each of yours . . . to a set of problems and a social commitment that is worthy of the time and attention given it here.
- But enough -- on the platform with me are seated those surviving among the cohort of chairpersons -- and the single group of feature players to whom this production will ever be most indebted.

Let us now hear the reports from their panels:



The Panel Chairmen are being given a two-week period to refine their reports, in order to reflect most carefully the views of their Panels. Therefore, we will not be releasing copies of the presentations you heard today. Instead the Secretary will mail copies of the revised draft Principles based on the chairmen's reports to all Conference participants by late November. In addition, the revised Principles will be the object of an independent critique by the Institute of Medicine representatives who attended all the panel sessions yesterday and today. On the basis of public comments and the IOM critique, these Principles will be revised by the Secretary, and the process of converting them to goals and eventual budgetary plans will begin.

## MINDING THE BIOMEDICAL CONTINUUM\*

by

Donald S. Fredrickson, M.D.\*\*

with

INTRODUCTION

by Dr. Evans

Wendell Scott, Professor of Radiology at Washington University and Mallinckrodt Institute, died of cancer in 1972 at the age of 66. A native of Colorado, his association with Washington University began in 1928 when he started medical school and it continued for his entire professional career. Dr. Scott's accomplishments and responsibilities are legend and the President's Medal of the American Roentgen Ray Society, the Gold Medal of the American College of Radiology, the Gold Medal of the St. Louis Medical Society, the National Award of the American Cancer Society, and included Distinguished Alumni Awards from the University of Colorado and Washington University. He held many important offices that included the Presidency of the American Roentgen Ray Society and he served as the national President of the American Cancer Society. He received honorary degrees from the University of Colorado and Washington University. This last degree was awarded after his death, and it was my privilege to accept this degree for Scotty and his family. Wendell Scott was my teacher, advisor, and friend. He was a great man and had the ability to involve himself in several important projects, yet give each his seemingly undivided attention. His hundreds of friends and colleagues have established a living memorial to his loyalty and excellence in the Wendell G. Scott Annual Lectureship at the Mallinckrodt Institute of Radiology.

Previous lecturers in this series have included Michel Tourbegosian of this Institute and noted scientist, Mr. Harvey Pickard, Dean of the Faculty of International Affairs at Columbia University and co-founder of the James Pickard Foundation, Christopher S. Bond, former Governor of Missouri; and Godfrey Hodgefield, inventor of computer tomography.

Our seventh lecturer has been Director of the National Institutes of Health since 1975. Like Wendell Scott, he was born in Colorado and received a portion of his undergraduate training at the University there. He received the M.D. degree from the University of Michigan, and served as a house officer at the Harvard Hospitals and the National

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\* Wendell G. Scott Lecture presented at Washington University, St. Louis, Missouri, on October 10, 1978.

\*\* Director, National Institutes of Health, Bethesda, Maryland.

Heart Institute in Bethesda. He is well known as a clinician, scientist, and administrator. His clinical and research interests are in the areas of lipid transport metabolism, medical genetics, arteriosclerosis, and health care systems. He has published more than two hundred articles and his textbook, The Metabolic Basis of Inherited Disease, is known to every medical student and clinician.

I first met our speaker when I served as a research associate to the National Heart Institute in 1966 and I can personally testify to his clinical research and teaching skills. His success in science has been matched by his accomplishments in administration. He performed an increasingly difficult series of leadership roles for the National Heart Institute through 1974, having served as its Director from 1966 to 1968. This included a time when the Institute's name and direction was changed to the National Heart and Lung Institute. He left Bethesda briefly in 1974 and moved only slightly to the southeast to become President of the Institute of Medicine in the National Academy of Sciences. In 1975, he returned as Director for all of the National Institutes of Health and has served in this capacity through three Presidents, and several Secretaries of Health, Education, and Welfare.

He currently serves on the editorial boards of the American Journal of Medicine, Circulation, Circulation Research, and the Journal of Atherosclerosis. His honors include the Gold Medal of the American College of Cardiology, the Distinguished Achievement Award by the Journal of Modern Medicine, the McCollum Award of the American Society of Clinical Nutrition, and the Award of Merit of the American Heart Association. He has received honorary degrees from the University of Michigan and the Karolinska Institut of Stockholm. He has agreed to speak today about "Minding the Biomedical Continuum." After his initial remarks, he has agreed to answer questions from the audience. Dr. Donald S. Fredrickson, it is my privilege to introduce you as the seventh Annual Wendell G. Scott Lecturer.

#### REMARKS

Thank you very much. This is the most persuasive man I've ever met. I swore I wouldn't leave Washington in October, but here I am. And I'm glad I did. Actually, the Secretary's office called me on Thursday and said, "You may not leave town until Congress goes out of session. All the agency chiefs are receiving this order." I called back and said of all the people the Congress needed least, it seemed to me, it was I, and on appeal was allowed to come. So that gives you a relative reflection of how important I am.

Mrs. Scott, it was a pleasure to meet you today and I'm honored to be here. Indeed, I didn't know Dr. Scott but of course meeting Mrs. Scott I understand something about him. People tend to reflect themselves in those they associate most closely with. He must have been a very fine



Now I agreed to come if I didn't have to prepare anything, and I haven't, although I've been preparing something for three years that cooks inside of me. I want to talk a little bit about my own impressions of the future of science in its present state, and I'll do that by reflecting on a series of episodes, if I may skip from one thing to another, and then I do hope to allow time for interchange, because in my position I think one of the most important things of all is to come out and see where the money is really being used. This certainly is one of the most productive gardens in which the Federal funds are being used to grow knowledge. Its fame has long preceded it. You know, I was out in Peking in July and I met Dr. Wu at the Cardiovascular Hospital. He's a man in his seventies, and like all that upper remaining eschelon of Chinese, the generation below them having been wiped out by the Gang of Four or the Cultural Revolution, like that older generation they have all been in America. Dr. Wu said, "Well, I studied in St. Louis," and something in me said, "Well, I'll bet you were with Dr. Graham," and he said, "Yes, I was, back in 1927." And he came back from that experience here to become the leading cardiovascular surgeon, or I guess he started out as a generalist as I guess was Dr. Graham. And then I went around and found that nearly all of his peers, too, had been in midwestern institutions. I hope to welcome the President of the Chinese Academy of Medicine sometime in the next several years so that I can fulfill a promise to take him back to Ann Arbor, where he spent his most formative years of postdoctoral training.

Let me talk a bit about the future of science, and let me really borrow from the ideas of three people that I heard quite recently at a meeting in Schenectady. You know, Edison is 100 years old—or Edison's light bulbs are 100 years old, or something—this year. I think it's that Edison, himself, would have been 100, and General Electric put on a symposium about the future of science a few weeks ago. They had three speakers at a panel, three really outstanding American scientists. Actually they're all in America now; one of them is British. The first was Victor Weisskopf, a professor of physics at MIT, whom some of you may know. You do, Mrs. Compton, don't you? He gave a lovely talk about physics, about quarks and leptons and icles, and discussed the future of that fascinating fundamental science. Weisskopf predicted that the next ten years in physics will be very disorganized, because they will be concerned primarily with amorphous systems, like extremely high energy states which might be so disorderly that they wouldn't even obey the laws of quantomechanics. A really remarkable talk. Physics is such a fascinating subject to those of us who don't know very much about it.

We went from those black holes of physics and its prediction of disorder to two other disciplines which its proponents said would become much more orderly. The first of these was chemistry, represented by Calvin from Berkeley, who as you know has worked so productively in many fields including photosynthesis. Calvin was all hooked on rubber



plants and substitutes for rubber trees, and this led him to a conviction that macromolecular systems and organization will be a major preoccupation of the chemistry of the next decade. He lamented the fact that chemists still must depend upon nature's own templates for synthesizing extremely complex macromolecular structures. The third speaker was Francis Crick, now at La Jolla, having left Britain—of course, as you know, a nobelist for the structure of DNA—and he went from that one dimensional discussion of base paring toward the new target, which is the target of his affections, that of neurobiology. That's where geneticists and molecular biologists are tending to move when they get tired of that particular field, hoping to lay a few tiles in the great mosaic of explanation of how the brain works, and clearly attempting to perhaps draw analogies with the extraordinary exposure of genetic structure which has been one of the really great products of the human intellect in the last several decades.

All of these people are extremely optimistic in the 18th century vein, as I think good scientists must be, and which so much of society is not anymore, if you want to have a belief in the future of science. And yet when they sat down together, under the chairmanship of the President of the National Academy of Sciences, they betrayed some of their concerns, particularly about the difficulties that they recognize today and foresaw increasing somewhat in the future in terms of having people in general understand more about what science is intending to do and how it's put together. Weisskopf thought perhaps that astronomy was particularly provocative of anxiety—those distant higher intelligences that someday we might hear and detect and become alarmed about. Actually, Crick said that astronomy is still a lovely thing for people; they can turn it off and on like a television set. It's biology that really frightens people because you're touching their lives: the way they think, the way they feel, their health. And so there you have one episode, a panorama, looking toward the future of science in its substance and suggesting something about the molecular organization of science or, should I say, its surface properties, its relationship to the rest of society where we may look for more disorderliness perhaps.

Let me now take you completely away from Schenectady to something more attractive—to Rome. Imagine, if you can, the beautiful American Embassy, La Tiverna, which is right behind the Villa Borghese, one of the most beautiful embassies we have, which is manned at the moment by a rather non-archetypal couple, Richard Gardner and his wife, both of whom speak Italian extremely well—he a professor of economics and law at Columbia—and we're going to sit down to dinner with 20 Italians invited for a provocative evening. The banter during the table, candlelight low, flowers beautiful, is not alarming. The man on my right describes the tortellini we are eating, the pasta, as something invented in Bologna and modeled after the navel of Lucrezia Borgia, and I passed this intelligence on to his wife who remarks about the sensuality of Italian approach to food. And

the whole party, after dinner, moved to a very spacious room for coffee and for discussion. The Ambassador lines everybody up around him and I am put on his right with an interpreter who speaks both languages to me, because I think communicating between people in Italy and the United States is not quite as easy as it is in some countries, even though the Italians don't need language to communicate a great many ideas and feelings in the first place.

The Ambassador asked me three provocative questions: "How much does politics enter into science in the United States?" "What about the problems of recombinant DNA and the new technologies to keep people alive? Are they causing problems in terms of people in America understanding science?" and finally, "How do people enter into the decision making in science in the United States?" Actually, I knew this was coming, because we had had a similar thing in Helsinki the year before with the Ambassador up there, and it was a remarkable evening, too. The Finns with all those thousands of miles of border with the Soviet Union are extremely circumspect and tend to be quite melancholy in the long winter nights. At that time it was the conclusion of every Finn that you can't involve the public in the discussion of science. There was only one exception: not the philosopher, not the poet, not all the other people, but the atomic physicist who said, "We've been there before, 30 years ago, and they understood after awhile."

So here were these same questions to a southern audience and how would they take it? I think I started off badly because I described the relationship of the United States Congress to the budget of biomedical research in this country. And no parliament—not the Bundesrat, not the British Parliament, not even the Presidium of the Soviet Union—gets more involved in determining precisely where it wants to put its emphases in biomedical science than does the Congress of the United States. I tried to convey this in a way that was not alarming, but it was clear when the President of the National Research Council in Italy raised his hand and said, "Stop." He said this was a frightening discussion because it suggested politicization of the scientific process to a degree that they might find intolerable in Italy.

Well, another Italian professor said—this time to his colleague—"I don't want to be known always as the enfant terrible of our circle, but let me remind you of two acts before the Italian Legislature. There are three, really, that count. They are Reformax, the Health Reform Act, and the Science Reform Act. The first of those is designed to create a national medical system out of a fairly innocent system currently existing in Italy. With it there will be created a council of 72 politicians and one scientist, and one of their duties will be to send to the National Research Council of Italy the priorities for health research in the coming year. The Science Reform Act will destroy the committee



structure of the current National Research Council of Italy. It will replace a council and committees now representative of the scientists and elected by them around the country by members half who are political appointments and half being elected by all the university professors, the majority of whom will not be in science. It is they who will then also determine priorities for the spending of scientific resources in Italy."

There was a rejoinder then by a politician from the Ministry of Health. Thus a colloquy began which went on until after midnight which illustrates that in Italy, like everywhere else, the confrontation between biomedical science and the continuum as we call it—the confrontation between that process and the adaptation of new knowledge which is derived from it to solve urgent and immediate practical problems in cutting down the cost of health and improving the efficiency of the system—is very real. And indeed as one goes across Europe, you find this same sense of urgency. This same tension is developing between people representing many sectors of society who want an improved system, who feel they can only guard health by a certain kind of new knowledge, a tension between them and the scientists who believe that these people do not understand the scientific process, how priorities must be related not only to need but to scientific opportunity; and that there is coming an increasing confrontation in these countries over this same problem.

Well, let's leave Italy for a moment—it's gotten very late there—and come down to my office where the telephone rings, as it did last Wednesday, and I'm told that a congressman is on. He's not on; I get on first then he comes on, and we tutoyer. It is unusual for us to use first name bases with congressmen that we don't see very often, but he started it and he said, "I hear you're trying to torpedo my amendment to this authorization bill," and I said, "I am not trying to torpedo it; if I were, I would let you know first." He said, "But you had a conversation in your office at 5:30 last night with one of the staff and here's what you said," and I said, "You're right, but remember I didn't go any further than your staff." But let me tell you our differences of opinion. And here's a very good congressman, one with whom I identify because he's a liberal and I think so am I, politically. He wants to make one of our Institutes monitor what the regulatory agencies, in which he does not have very much trust, set out as standards for compounds that may cause cancer. I don't like it, because I think that one of the gravest dangers to a scientific organization is that it will lose its objectivity when it engages in the inherent conflict of interest that is regulation. And I say "Mr. so and so" or "first name so and so, I don't like it because I think it puts us in jeopardy, and I suggest this as the alternative." And he doesn't like it and we argue and he says, "Can I go back to the floor and say that you will agree with either language?" and I say, "Yes," because my authorization is at hostage, and he knows it. If he doesn't get his way and he's right, that is the way the game has got to be played. We may not get authorization to continue some things that are very important

to you. Now, he's all right but we have a very strong disagreement. It's out on the table, and I want to give you this episode only to illustrate—not that I talk to congressmen every day—I don't. I've been to the 95th Congress 34 times in a more formal relationship. There is that same tension, then, in our own country; the same tension to make science work, to meet urgent perceptions of social need, in this case—for regulation.

Talking of telephone calls, let me tell you of another one I had in December 1976. Late in the evening, some of my own staff and I were huddled around a conference telephone box, talking to an advisory committee to the City Council of the City of Cambridge on biological and medical experimentation. We talked for an hour, answering questions back and forth about the esoterica molecular biology (I had some real experts with me) down to the minute details about the NIH Guidelines for Recombinant DNA Research. These were laymen and the conversation was very instructive to me because it showed that in matters like this, matters like the new power of biology, society has every right to know and an undeniable need to understand. And a community like that is determined to make the essential communication. Here we have, then, another aspect of biology, its apparent new powers—the powers in this case of genetic recombination and the possibility of the creation of new forms, I think wildly extrapolated at present into the ability to change larger organisms and particularly including man. But whether real or speculative, this kind of power of science, the power that is real and not speculative, that came out of atomic fission, the duplicity of some compounds to work for man on one side and endanger his life or his environment on the other, all create new problems between science and the rest of society.

Well, this has led me to think a great deal about something which I've called the public governance of science. Fortunately, the New York Times is dark; they don't like the word governance and refuse to use it anymore, but I think it's not a bad word. Does the public really govern science? Well of course it does because it pays for science. Science is much too complicated, too expensive, too sophisticated. It cannot be underwritten anymore by private sources, by endowments, or by institutions. In smaller ways that are extremely crucial to maintain the plural sources of support for education and science, they are absolutely crucial. But behind it must come a tremendous investment of money from the State. There are some very modern problems created by modern science—problems that certainly did not exist in the minds of Descartes or Bacon, those fathers of science. They didn't exist in Newton's time; all of Newton's ideas didn't threaten the British exchequer or safety of the environment one minute. Maxwell's demon was not put in P4 containment. Even the Copernican heresies went unprosecuted for at least one century, they weren't very dangerous either. But that's not true of some of the technology of modern science—or some of the potential technology. I think we are at a time when there needs to be extraordinarily careful articulation of just what it is that science is about, and a clear understanding on the part of both scientists and the public as to who is in control, and how far and what is involved in regard to these processes.



As you are aware, perhaps the greatest single problem today is that we are in a period where the resources are more limited than they were ten years ago. The support of biomedical science is not expanding anymore in the United States—it is stable, holding its own, and I regard public support as still very generous. But the question is, how are we going to meet all these new demands for urgently required new knowledge by a system that cannot expand, without tampering with one piece of it or another, and without possibly harming its capabilities? Well, one of the people who has become aware of how important is this question of the funding of health research is the Secretary of Health, Education, and Welfare. And last week, Bill Danforth and other pilgrims came to Washington to participate in a National Conference on the Principles of Health Research—a really daring and uniquely American exercise. They were attempting in two days to hear from the public, large numbers of public witnesses and through committee process, to arrive at a description of what it is we want to underwrite from this point on to reaffirm old principles and perhaps to create new ones which might bear on the organization of the budgeting of biomedical science. There were five panels, and I will not attempt to give you the product because you'll get it in one form or another as the months of November and December come around. But let me tell you a little about what went on. The first panel was on fundamental research, and, like all the panels, it was chaired by a distinguished person who knew what the score was, who understood better than his panel members because only he or she had been aware of what this process really entailed, and on fairly short notice. But there were 15 or 20 people trying to interact and to develop a set of agreed-upon principles underlying their particular area. The fundamental researchers were pretty monoclonic; that is, they were one phenotype. They were all successful in the laboratory because they are kept innocent by the nature of the process—a very important process and a very important protection, the process of protecting many institutions from much of the political tension that exists. You know there is a certain morality in science which really makes it very difficult to mix objective judgments based on orthodox lines of truth with value judgments. Monod talks about it in his book. He takes a very single-minded line, but he's right in the sense that the tension exists and you create apostasy when you cross over. That's why particularly these fundamental scientists, I think, need to be kept away from some of these problems that lie at the interface. But it certainly does make it difficult for some members of that persuasion and that experience to really understand the competition or the difference in views of perception of why society should support fundamental research and to what extent. I don't think anybody is attacking basic science. Everybody knows you have to do it. Every politician I've ever met understands it. But every politician I've ever met is also listening to other constituents who have more immediate needs and trying to balance the level of support for this

quiet enterprise which has invisible promise against something that will tomorrow, perhaps, appear to be an important solution. That balancing is very difficult. I'm afraid I even had to scold the fundamental research panel, and I just wrote an apology to them before I left last night. I said, "You don't explain why you must continue to do fundamental research. You just assume everybody knows. But everybody doesn't know. You don't explain why you biologists need to do this kind of work or much of it in the form of a continuum; one that is not necessarily directly related but is not divorced completely from its eventual application for the betterment of man—some development or practical application." So much for fundamental research.

The next panel was Clinical Application and Health Service Research. Nothing in this country stirs up more excitement among politicians than health service research. Nothing is done so badly in this country, and the others that I know of, than health services research. What is it? It is the research that tells you how to integrate single interventions to keeping populations moving, to running a hospital, to making them efficient and economical. You do that very well without a lot of health services research. You get it in that institutional way. But there are many national questions which arise immediately upon nationalization of the health services which are going to again seem to be so demanding that every effort will be made to mobilize all kinds of science to try to answer some of those questions, not all of which can even be answered by the scientific method. Well, the Clinical Applications group went about its business fairly briskly. They came up with a lot of things which will make interesting reading when you see the fabric. Certainly, they endorsed a biomedical research continuum. Feeling that this is the best way, you must couple these activities. And it's very important for all of you because it means that almost certainly they are right. You have to couple support for fundamental biology and clinical application. And when you do that, you create another source of tension, because people want to know: is this intervention? this operation, this drug the ideal thing, is it better? is it good? To find that out, you commit millions to clinical trials—hundreds of millions, potentially. If you do that, you then have to ask yourself, "Are we leaving unprotected and inadequately supported the area of fundamental research?"

The third panel was Health Regulation and Promotion. And here's the biggest single source of tension in Washington today. The regulators want more knowledge, and they don't think that you academic scientist types, or I, the archbishop of this diocese, pay enough attention to their needs. Perpetual unresponsiveness, they say. We want more fundamental mission-oriented research toward the needs of regulation. And this is not resolved yet today. It is not resolved in any country that I know of. But it is a big issue here today and I hope to see whether the final report of that panel goes further toward resolving it than it had done at the time we heard its first response, because this is really a very tough question.



How do you get the information that the FDA wants about the Delaney Clause? More importantly, how do you get the information the EPA demands because of TOSCA. Laws have been written which mandate a degree of wisdom and knowledge which we simply do not have. How do you get that? By doing away with half of neurobiology and putting all that energy and creativity into the direct line of testing for carcinogenesis? Nobody knows, because here the dynamic of the research process, the individual contribution and the importance of his or her selection of problems, part of the energy drive, is very much at stake.

Panel No. 4. I don't need to tell you about that. It was headed by a man by the name of Danforth. Extraordinarily well headed, I can say without flattery, but very important because this research capability group really was trying to analyze the long-range questions of institutional stability, of support, of training, of mechanism. Here I think, now that we've stopped expanding but have come into a stationary phase as far as the growth of the system is concerned, lies one of the greatest and most important areas of the immediate future. How do we change our mode of giving you grants? How can we shorten those applications, make them smaller? Can we give awards that are longer than three years? Why not? Can we award to institutions? What happens when you do that? How will you create solutions to the obsolescence of some plants? How will you make equipment be better shared? How can we be more efficient? All of these questions will be dealt with by that panel and I, as well as you, will be very much interested in its preliminary report.

The last was the panel on Unifying Concepts, sort of getting it all together at the end, knitting up the raveled sleeve or something of that sort. Well, it had to report before hearing all the others, or it hadn't time to think. But here are the basic questions that also relate, a reaffirmation of society's need to support research; perhaps some statement about the limitations of what science can do for you as a citizen, what you have to do for yourself; some talk about this regulatory process, this demand for decision when you don't know enough; the tensions on the scientific system which are created by the demands for mixing value and objective judgments. Other ethical issues, of which there are many, include the question of the sovereignty or the lack of sovereignty of science—the relationship of other institutions to science, like the law, the administration, and the Congress. All of these things will need to be attended to if there is to emerge from this exercise some kind of new proposal for a long-range budget to help the nation make a more stable and longer-range commitment to the support of science. There are, then, many tensions between science and society. There have always been, but I think there are a number of reasons for the rationalization of health systems: its rising costs; the new power of biology and of medicine to change the quality—perhaps even the character—of life, the

increasing threat to the environment which we create in our endless search for more energy; the tests between the adaptation of the individual and of populations to this changing environment. All these are reasons why there has to be a continuing health to the process of science, and also why we will have to learn and have to solve some of the problems at the interface. I think there are a number of responsibilities on both sides. Clearly science needs to better understand those institutions which basically control it. It needs to speak well. Scientific advice has to be freely available to government in a thorough and understandable form. I want to urge you to recognize that the wisest and the most gifted must not be reticent in speaking, because when you remain silent there are lots of self-serving and less competent people to take your places at the forums where the record is created and the decisions are made. The public, I think, also has a responsibility on its part to try to better understand and to be helped to understand the physical and the human capital that make up the nation's capacity for research, its perishability, its organic nature, and the ease with which this process can actually be stifled by inflexible regulation or unthinking demands for discovery tomorrow. I think that the interests of the public and of science certainly can be served jointly. They are both components, after all, of a greater whole. Indeed, I think they must be served if our earthly presence is to continue to be preserved. Ways certainly will be found; adversary processes don't need to imply totally adverse interests, and I think that man's genius for discovery is matched by his art in compromise.

Frankfurter wrote Judge Bazelon, once, in a postscript to a note, "What ties people in friendship is not identity of opinions but harmony of aims." And in biomedical research, all of us can come into harmony if we take the time and trouble to understand what it's all about.

Well, I think, Dr. Evans, that that is all I want to say in a formal way, and I'll be glad to answer some questions—or taunts, if people want to throw them.

## QUESTIONS AND ANSWERS

Dr. Evans:

Dr Fredrickson has indeed agreed to answer questions or taunts, and if there are too many taunts, I'll step to the right, Don. We will finish by 5 o'clock but we do have some time and I open it up to the audience.

(Questions are not audible on the tape; but this is transcript of Dr. Fredrickson's answers)



1. I'm not sure that I can answer all of your questions. I can tell you some things. The new Administrator of FDA is a very good man, a very capable person. Although Kennedy and I don't always see eye to eye—that's an understatement—I certainly respect enormously his capabilities as a scientist and as a person. You know, some of the problems of the FDA are the problems of the American people. They haven't made up their minds about this *parens patriae* principle. How much do you want the government to make your decisions, to protect you? In the laetrile issue, we see an overthrowing of that. I'm not sure how much of a thoughtful overthrow or gesture that is but you see a reaction—people insisting that they want to make some decisions. That's probably not as tough a call as something like the Delaney amendment, where we find the Congress constantly writhing in uncertainty as to really what it wants to do about so rigorous and really so unmanageable a piece of law as that amendment. Unmanageable, because now we have the technology to detect parts per trillion of everything and in everything, that we eat. To extrapolate that material, which may in very different settings cause cancer, to an elimination of it really poses problems that are of another dimension. But the problems of FDA basically are the problems of the people. The regulators are only out there doing what the law tells them to do, believe it or not, and they have a hopeless job. I wouldn't want it for the world, because there isn't any maybe in regulation. Either yes we have to regulate, or no. And you simply can't often come to conclusions on the basis of reasoned available knowledge, so that I wouldn't push hard on the bureaucracy; I'd push on the people and on the Congress. What do you really want? If you want more or less total protection, then you will have to accept some excesses in regulation. So that's how I feel, in a very brief answer, about part of your question.

2. Well, this is the key. How do we do this? How do we meet the need without destroying the providers? There clearly has to be some way of leading people who are in the mainstream of science toward these urgent practical problems. There's got to be a constant conversation—not constant but frequent—between those who have problems that must be solved and those who might have an idea of solving them. The idea that scientists don't care about practical or general use of their inventions is ridiculous. Nobody can find a cure for cancer fast enough. We all want that, because recognition is the great reward for scientific achievement. But, you know, there is a problem of creating the solution, if I may, to the metaphor in Aristotle's use of the word, that is the connection between distant things. You have a problem and I might have a solution. Now, somehow we have to facilitate our getting together. The alternative would be to try to create large forces of people who will be occupied only with those immediate problems. To me, there's a great danger that that might move away from the mainstream of creativity, from the driving energy that is the genius of the investigator-initiated idea. It's the driving force, the creative engine. But if we don't have great warehouses of people working only on these very practical things, then we shall

have to see that the garden and the need for produce are very closely coupled. We really have to get together somehow. Now we are trying this on a small scale with toxicology testing. We've had quite a tiff in the Department. How do we do this? Do we put it in the research agencies? Let them have responsibility but work with the regulators so they feel that they are getting response and care for their problems? Or do we keep the researchers away from it because they must not become tainted with these practical problems and let the regulators go about it? Well, I think we're coming up with a solution where we'll have an amalgam of these two, and I hope the Secretary gets around to announcing that. That's a very small experiment in this much larger problem, but that's how we have to begin. I don't know the complete answer to your question; in fact, I would guess that's the biggest single question vis-a-vis the organization of health research in HEW.

3. Well, in part this has been temporarily answered, as far as how far the NIH should go, I think, in that the Department has set up its own office of health technology for the purposes of managing technology, and that's a real semantic problem, isn't it? How do you manage technology? Basically, upon coming to NIH, and it was my first great problem. I thought, what is the real boundary, how far do we move it out toward solution of these problems? I think that we had to show that scientists are credible, that they care, and I felt that science is essential in one part of this process, that is, evaluating the state of the art. What is it we really know technically? Hence, we've launched these technical consensus exercises which have been very interesting experiments and not always totally successful. But we have attempted to catalyze the getting together of the necessary group to develop the state of the art about any particular invention, or some particular invention, so that then other groups, other pieces of society, other parts of government, may lay their value judgments on; I think this is a minimum response. I think it's pretty close in some ways to the maximum, because there is a limit to the degree that the technical person should attempt also to make the value judgments. He should not. There is a limit to our wisdom, but if we can get out there what we really know so other people can operate on it, that will be an important service. I think that's one thing we can do better than we have in the past and I think we're beginning to do it.

4. Yes, it's absolutely essential. It's the old Santiana thing, you know. You've got to understand what we've just been through to keep us from going through it again and again. That won't always work, but science and its relationship to the rest of society are now in a stage where social analysis can be very useful, so we can all understand just what it is that we agree upon, and where we might disagree. I think that it's urgently needed for wise analysis and discourse of this kind, because if you injure the capability for science that we have created in this country, you will never get it back. We couldn't afford it. You simply can't do it.

5. Well, I can't answer that question any more wisely than the rest of you can. It would be a parochial answer. I will tell you this, though, that no form of news medium meets its full responsibilities in reporting science today, television least of all, and very few newspapers come up to it. The discourse, the description, the understanding which these media offer to people about science is completely inadequate and very often warped. For harsh, economic reasons, they're selling news; they're selling time, commercially; and they have to compete. To do that they're dealing with our lesser instincts, our meaner base, scandal, and so forth. You, as a person in the public, can never learn enough accurate information about science from any of the popular media. Unfortunate, because what more important topic could there be from the standpoint of a scientist?



by

Donald S. Fredrickson, M.D.<sup>2/</sup>

Good evening, ladies and gentlemen.

I am most happy to welcome you this evening and to introduce to you Dr. Frank H. Ruddle, who will present the 26th lecture commemorating the contributions of the late, former NIH Director, Dr. Rolla Eugene Dyer.

Dr. Ruddle is Chairman of the Department of Biology and Professor of Biology and Human Genetics at Yale University. He has served at that institution with distinction since joining the faculty 16 years ago.

Dr. Ruddle received the bachelor and master of science degrees at Wayne State University, was awarded an NIH fellowship in 1958, and received the Ph.D. degree from the University of California at Berkeley in 1960.

Among his many honors are the Presidency of the Society for Developmental Biology in 1971, the selection as a Harvey Society Lecturer in 1974, and election to the National Academy of Sciences in 1976.

Dr. Ruddle's research career has been devoted to the study of somatic cell genetics. At Yale, he directs one of the most productive laboratories in this field in the world.

In his lecture he will discuss new technologies and rapidly expanding opportunities for greater understanding of complex mammalian genomes. One of the commanding challenges in his laboratory is mapping the human genome; that is, the assignment of specific genes to specific locations

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<sup>1/</sup> For presentation at the Dyer Lecture, 8:15 p.m., October 18, 1978, Masur Auditorium, National Institutes of Health, Bethesda, Maryland

<sup>2/</sup> Director, National Institutes of Health



on one or another of the 23 pairs of chromosomes. The location of about 200 human genes has now been identified and progress in the field is rapid.

Until recently, the assignment of genes to specific chromosomes has required both knowledge of the product coded for by given genes and a means to assay its expression. Many genes, though, are "silent," either because they are not active in a particular cell or, because if they are, we do not know what their function is. But the coupling of recombinant DNA technology, nucleic acid hybridization, and other new procedures with somatic cell genetics is making it possible to map even the "silent" components of the genome.

Tonight Dr. Ruddle will speak on "Gene Transfer in Mammalian Cells."

Dr. Ruddle.

## REMARKS\*

at the

## PRESENTATION OF THE GAIRDNER AWARD\*\*

(to the best of my recollection)

Chancellor Moore, President Hollenbeck, Ladies and Gentlemen:

When you next go to Moncton, it's not much further to Apahauque. Once you're at Apahauque, you might as well go on to Lower Millstream. When you're there, look for McVey's Creamery. Bear left there at the fork and in a few turns you'll overlook the Sharp homestead. Here my forefathers have earned their living from the soil since before the Revolution.

It's probably a good thing that my Grandfather Sharp has passed on now. He died at 93, more than 80 of those years behind the plow. It would be very difficult to explain to him this prestigious thing you've done to me tonight. "I don't understand," he'd say, "why those people in Toronto have given you all this money. You're a doctor and you've never worked an honest day, sitting around solving puzzles." "Besides, you're only a half-a-Canadian."

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\* Given by Donald S. Fredrickson, M.D., Director, National Institutes of Health, Bethesda, Maryland 20014.

\*\* Presented by The Gairdner Foundation at the Royal York Hotel in Toronto, Canada, on November 4, 1978.

I'd try to explain to him how those people in Toronto, especially a wise man by the name of James Arthur Gairdner, had realized that:

- scientific research was international;
- what maintained excellence in science was a continuing self-criticism of everybody in it by the whole community of scientists;
- that, every so often--they also realize that the singling out for recognition of a few samples from the whole number who pass this collective review had a critical influence on the continuance of momentum and the striving for excellence of the system.

On this basis, I'd say to Grandpa Sharp, James A. Gairdner made his wise and generous bequest. Perhaps it was a bid for that touch of immortality which we all covet. And if he has reached it, then perhaps we who have been chosen to honor his name will have our chance at it, too.

I am extraordinarily proud of this award and I accept it in the name of the many gifted colleagues who have earned it with me. Thank you very much.



# The National Institutes of Health Yesterday, Today, and Tomorrow

DONALD S. FREDRICKSON, MD

IT IS A PRIVILEGE TO CONTRIBUTE to *Public Health Reports* in its 100th year. Like *PHR*, the National Institutes of Health looks back on almost a century of history, having had its start some 91 years ago in a one-room laboratory in the Marine Hospital on Staten Island. There Dr. Joseph J. Kinyoun, founder and director of the Laboratory of Hygiene (it became the Hygienic Laboratory in 1891), introduced scientific research into the Marine Hospital Service. His work in bacteriology and isolation of the cholera organism laid the groundwork for the present biomedical research programs of NIH.

## Growth Before the Present Decade

The National Institutes of Health is the principal medical research arm of the Public Health Service. It is today one of the largest medical research centers in the world. For its first 60 years, however, its function was purely intramural as it served essentially as the laboratory for PHS operations. It began with activities in nutrition and microbiology, and early in this century it was made responsible for biologics standards in the country (subsequently transferred to the Food and Drug Administration in 1972).

Over the years the responsibilities of NIH grew slowly. It had its first big spurt of activity immediately after World War II. The Public Health Service Act of 1944 gave NIH the legislative basis for its post-war programs and began the major Federal commitment to the support of biomedical research—something unprecedented in the history of this country.

Few people realize that before World War II the support of science was not regarded as a responsibility of the Federal Government. Those of us who



Joseph J. Kinyoun, MD (1860–1919), who joined the Marine Hospital Service in 1886, was director of the Hygienic Laboratory from its establishment in August 1887 until April 30, 1899

remember the excitement that followed the successful splitting of the atom can recall vividly the national mood it inspired: that brains and money could accomplish miracles. In common with other science agencies of the Federal Government, NIH was a beneficiary of this national spirit.

The advent of space flight in the mid-1950s gave a further boost to science and technology. NIH entered a period of unprecedented growth. Each year from 1957 to 1963 the NIH budget increased by an average of 40 percent annually; appropriations grew from \$98 million in 1956 to \$930 million in 1963. There was a 12-fold expansion in grants to academic insti-

*Tearsheet requests to Dr. Donald S. Fredrickson, Director, National Institutes of Health, Bldg., 1, Rm. 124, 9000 Rockville Pike, Bethesda, Md. 20014.*



tutions as the result of a deliberate congressional policy to expand the U.S. capability for biomedical research by rapidly increasing

- Funds to support research projects
- Federal assistance for the construction of research facilities
- Fellowships and training programs for research manpower
- Support for research abroad—to a limited extent.

By 1963 the United States was preeminent in biomedical research. NIH made grants to foreign institutions and had offices in Paris, Tokyo, and Rio de Janeiro, from which the seeds were sown for a renaissance of biological research in the developed countries of the world. But the geometric progression of 40 percent annual increases clearly could not be continued—in another 7 years it would have brought the NIH appropriation to \$8 billion.

The growth of NIH slowed markedly. In fact, the latter half of the decade of the 1960s has been characterized as an era of no growth. The average increase in funding was a little less than 6 percent in those years, construction funds ran dry, foreign grants were sharply curtailed, and the number of research grants began to fall.

### **The Current Decade—Selective Growth**

The 1970s have had a different character, marked by narrowly mandated and selective growth. The decade began with a widely heralded campaign to mount a war on cancer. After enactment of the National Cancer Act of 1971, appropriations for the National Cancer Institute trebled in 4 years. This funding permitted needed growth in several basic disciplines then ripe for expansion: genetics, immunology, cell biology, and virology—all areas relevant not only to cancer but to all of the life sciences and medicine.

This legislation was followed by the National Heart, Blood Vessel, Lung, and Blood Act of 1972, an act reflecting the new and expanded interest in diseases of the lung and of the vascular system. In that year also, new legislation emphasized further support for research and training in digestive diseases and added a new title—the National Institute of Arthritis, Metabolism, and Digestive Diseases—to an old institute. The Research on Aging Act of 1974 brought an 11th institute into the NIH complex. The new National Institute on Aging was authorized to support not only biological research, but also social and behavioral research related to the aging process and the special needs and problems of the aged, thus adding a new dimension to the programs of NIH.

This era continues to be one of intense public and Congressional interest in specific diseases. Laws have been enacted that call for increased research on Cooley's anemia, multiple sclerosis, sudden infant death, diabetes, arthritis, Huntington's chorea, and certain communicable diseases. Congress has thus become more closely involved in the setting of research priorities.

Although this kind of interest is welcome, it can also be unsettling. Support for some areas that are not so visible or that do not command popular appeal (for example, endocrinology and metabolism, kidney research, and hematology) tends to decrease. The National Institute of General Medical Sciences, set up to fund basic medical sciences, and also the National Institute of Allergy and Infectious Diseases, have lost about 10 percent of their purchasing power in recent years.

### **Recent Innovative Actions**

This brief historical glance at the evolution and direction of NIH offers very limited opportunity for useful speculation about the future. Nonetheless,

some recent developments at NIH related to administration, programs, and policy will certainly influence its course in the years ahead.

For example, NIH has been intensively reviewing its peer review system—at one time a unique experiment in self-discipline and quality control in the distribution of public funds. For 35 years this system has served the scientific community and the public well. Neither excellence nor sound stewardship has been compromised, and the return on the public investment has been substantial. Nor has there been any real challenge to the system, only a certain discomfort with it.

As most readers of *Public Health Reports* are aware, the system originated at NIH in the late 1940s. It consists of a two-tier peer review system. The first review is conducted by specialty scientists, who assess the technical quality of research proposals. Then advisory councils, which include members of the public as well as health professionals, judge the proposed project in terms of its potential contribution to the prevention and cure of disease.

In recent years the system has come into question on such issues as possible conflicts of interest, the reappointment of distinguished people by an alleged “old boy” system, favoritism to investigators at distinguished institutions so that the rich get richer, the secrecy of deliberations, and the finality of a system that provides for no intercession and no appeal.

In 1976 NIH undertook its own internal review of the peer review system. Public hearings were held in Chicago, San Francisco, and Bethesda, Md., and written comments were obtained from present and former non-Federal members of review bodies as well as from applicants, grantee institutions, and the general public.

The peer review study team submitted 69 recommendations. After consideration by a small working group of senior staff members and program heads, 33 of the recommendations received outright approval, and 9 others were approved with minor modification. Action on 19 proposals was deferred pending additional examination and discussion, 3 recommendations were rejected, and 5 required no action.

One set of recommendations that was adopted is designed to improve communication with applicants. It requires NIH advisory councils and boards to promptly provide all applicants with the complete summary statements or critiques of their proposals, including priority scores, once final action is taken.

Another set of proposals that was adopted is aimed at opening up the process for nominating and selecting non-Federal advisors for service on councils and

initial review groups. NIH is also committed to assuring that women and members of ethnic minorities who qualify as experts have maximum opportunity to serve on advisory groups.

Pending further study of a group of recommendations to establish a formal grants peer review appeals system (to include an ombudsman), decision was withheld to enable further evaluation of the implications of such a system vis-a-vis legal, financial, and personnel resources. Meanwhile, interested members of the scientific community, including readers of this article, are free to offer further recommendations and suggestions.

As to program developments, the public continues to make known its concerns about unsolved problems or areas in which scientific knowledge is scanty. One such area that has caught the public's attention is nutrition. Leaders in Congress have been especially vocal in their call for more concentrated efforts in nutrition research.

Reflecting this national interest, NIH has mounted a number of specific programs in this area. The National Institute of Child Health and Human Development is launching a new program on clinical nutrition and early development. At the other end of the age spectrum, the National Institute on Aging has begun its own program in clinical nutrition and at



In a laboratory in the National Institute of Child Health and Human Development, an atomic absorption flame spectrophotometer is being used to investigate nutritional abnormalities



a 3-day conference in June 1978 brought together some of the nation's outstanding clinical nutrition experts to discuss the nutritional needs of the aging adult.

Also in June 1978, the NIH Nutrition Coordinating Committee sponsored a conference on the "Biomedical and Behavioral Basis of Clinical Nutrition: A Projection for the 1980s." Leaders in nutrition research in this country reviewed biomedical and behavioral nutrition research, related this research to current clinical practice, and helped project the future frontiers of nutritional investigation. Participants from other government agencies, academic authorities on nutrition, members of congressional staffs, and consumer advocates affirmed the need for new knowledge about nutrition and wide dissemination of that knowledge.

A "consensus development" conference on the surgical treatment of morbid obesity is scheduled for late in 1978; another such conference also is planned to draw up recommendations on total parenteral nutrition and hyperalimentation—subjects of great interest and some controversy at present.

Subsequent consensus conferences will provide a mechanism for seeking professional agreement upon the clinical significance of new medical procedures. The idea is to bring together a variety of points of view on new or controversial procedures and to have an open and extensive discussion of their advantages and drawbacks. In this way it is hoped to speed the transfer of technology from bench to bedside and thereby to assure that pertinent and valid information is put to work as promptly as possible in improving patient care.

In fact, NIH held its first consensus development conference last year. At that meeting, which focused on the use of mammography for breast cancer screening, consensus was reached that routine use of mammography should be limited to women 50 years of age or older. The success of that conference has encouraged NIH to make subsequent use of this device to speed health policy decisions.

In some areas of science and research, particularly those with important social and ethical implications, the public must share in the planning and development, right from the beginning. An example is the advent of DNA recombinant techniques in microbiological research. And almost from the beginning, the public has been involved in helping NIH formulate guidelines for the conduct of such research.

Concerns about the safety of recombinant DNA research were called to the attention of the scientific community and the public by scientists themselves—



Researchers at NIH's P-4 containment facility at Fort Detrick at Frederick, Md., use shoulder-length rubber gloves to move and control all materials. The facility is the first recombinant DNA research laboratory certified to meet NIH guidelines

I know of no similar situation. Some of those who originally expressed misgivings about such research have now concluded that their fears were exaggerated and, in an about-face, have come to oppose government regulation of it. But it is to their credit that they freely shared and aired their doubts and in the process of doing so, made a historic contribution to the public governance of science.

With the participation of many individuals and groups—scientists, lawyers, ethicists, environmentalists, and consumer advocates—in June 1976, the NIH formulated guidelines governing the use of DNA recombinant techniques. These guidelines are at the present writing undergoing revision. It is hoped they may (a) exempt from regulation certain classes of DNA experiments, (b) strengthen institutional authorities in determining compliance with the guidelines, and (c) for the first time make provision for private industry to register voluntarily its recombinant DNA activities with NIH. It is still uncertain whether legislation will be enacted that will provide the regulations with the force of law to govern such experiments. Nevertheless, whatever happens, the conduct of the scientific community in this matter has been responsible and in the best public interest.

### Planning Future Research

There is no doubt that this nation is firmly committed to basic biomedical research. Both President Carter and Secretary Califano have reaffirmed that



commitment, as have leaders in the Congress. But policymakers and administrators alike are faced with the enormous dilemma of maintaining the momentum of research in an era of shrinking resources.

Maintaining that momentum will take skill and patience and prudent planning on the part of all concerned. In a wide-ranging and very supportive speech earlier this year, Secretary Califano suggested the development of a multi-year plan for health research. By the time this article appears, we at NIH will have held the first of what may be a series of conferences—shared in by scientists, health professionals, and the public alike—to define the principles on which such a multi-year effort should be based. We have already been giving thought to directions for the future, being well aware that we must constantly hone both the form and function of our programs.

One of the problems is defining basic research. There is considerable confusion and disagreement, even within the scientific community, as to its character and boundaries. In an effort to avoid this impasse, and for ease in planning, we have classified our activities under four major headings: science base, clinical application, training, and transfer. We are using these concepts in both program planning and budget development.

**Science base.** Under the science base umbrella, we include all those elements that contribute to the search for new knowledge about fundamental processes—grant support for research projects (NIH has about \$800 million in research grants) and program projects, some center-based activities, some intramural research efforts, some research contracts, and some special resources.

**Clinical application.** Clinical application involves the further development and assessment of knowledge for immediate practical purposes. Clinical trials, the largest element in this category, are prospective research activities undertaken to assess the value and effect of agents, devices, and procedures on human subjects (NIH has some \$200 million in this activity). In addition, research on the development of vaccines, other biologics, drugs, and devices also qualifies, because the outcome of such research yields knowledge immediately applicable to human beings.

**Transfer.** The transfer sector of the research continuum includes five activities—demonstration, control, education, consensus building, and dissemination. Part of the responsibility of the research

community is to transfer new knowledge promptly to the health professionals who can put it to work.

**Training.** Without a consistent flow of new investigators, the future of biomedical research would surely founder. Promising young people must be found, motivated, and trained for careers in biomedical science.

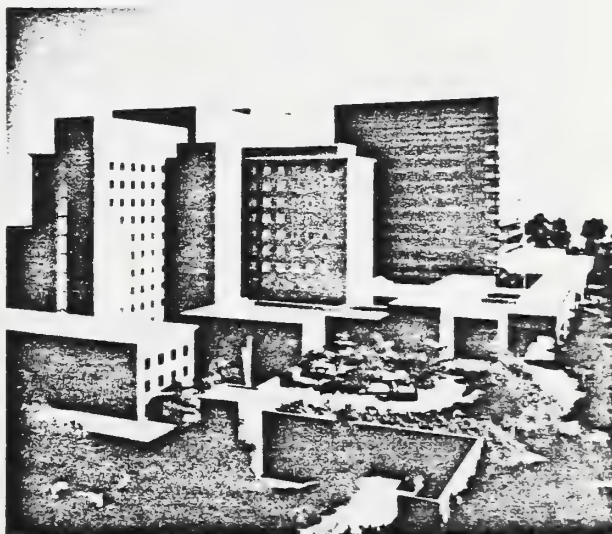
At a meeting of the NIH Director's advisory council at NIH June 16 and 17, 1978, major issues emerged that the Department of Health, Education, and Welfare may wish to address in future long-range planning of health research and in arriving at principles suitable for guiding such a plan. The outcome of this activity—in which other Public Health Service agencies have also been engaged—will help set the planning agenda for health research in the future.

### Future Funding of Research

Consideration of what the economics of biomedical science will be tomorrow evokes a beautiful illustration of what Voltaire was talking about in his *Dictionnaire Philosophique*, when he stated, "It is said that the present is pregnant with the future." We can never be sure what era we are bringing to birth, but we want to assure that the capacity for exploration is kept strong and that the ultimate development will be in the public interest.

Three questions about biomedical science may pertinently be asked at this point:

1. Is it likely that we will return to a parochial period in which resources will be derived primarily from private sources?



When completed, the new Ambulatory Care Research Facility being constructed on the NIH campus at Bethesda, Md., will accommodate an estimated 300,000 outpatient visits each year



The answer is assuredly negative. The Federal Government has not become disenchanted with nor disinterested in research. But research must compete with other desirable health programs and goals. And some of these other programs, because the problems related to them are perceived as being more immediate or more serious (the costs of and access to health care come to mind), may have a higher priority at the moment.

2. Are we headed for another period of exuberant growth or unselective expansion?

The answer is almost surely just as negative, partly because there is greater competition for limited Federal funds. Also, a drop in school-age children will curtail university expansion. Moreover, there are also clear signs that the always small fraction of medical school graduates interested in research as a profession is, at least temporarily, diminished, in part because of deep concern about the stability of support for such a career. And we are groping for ways to attract bright young minds into scientific inquiry.

At the same time, it is worth noting that at this writing, the NIH reservation is reverberating with new construction, which in itself is a foreshadowing of things to come. The new 13-story Ambulatory Care Facility will expand and strengthen the combined laboratory and patient care programs of the Clinical Center, our research hospital. When completed in the early 1980s, the new addition will be able to handle an estimated 300,000 outpatient visits each year, nearly 3 times the current figure.

At the other end of the NIH campus, the 10-story Lister Hill Center building will be a part of the National Library of Medicine. When it is completed in 1980, the building will house the communications technology and network programs of the new National Center for Biomedical Communications and the closely related functions of the National Medical Audiovisual Center, presently located in Atlanta, Ga.

Finally, there is a third question that should be asked:

3. If maintenance implies increasing selectivity, what are the future funding strategies?

The answer is compound: one part concerns the political imperatives; the other, the allocation of resources within institutions for the conduct of scientific inquiry.

First, biomedical science is preeminently humane in its objectives, and it must consciously adjust to its patrons' expectations and needs in every way that does not destroy the process of discovery. There must

be practical, useful results emerging: that is the essence behind the labels "technology transfer" or "consensus development."

Science must prove itself capable of self-governance in regard to laboratory safety and other issues in which the public has a vital stake. The controversy that has swirled around the subject of recombinant DNA research has been a profound experience for scientists, for NIH as an institution, for the Congress, and for the public as a whole. If science fails to govern itself, regulations and laws will descend upon the laboratories, and science may find itself tragically fettered.

At the same time, within scientific institutions there must be adaptation and accommodation, and there is a rather narrow limit to the rational management of science through the allocation of resources.

## Conclusion

Society will continue to set mandates for biomedical research—as patron, that is its right. Those who administer the research funds have to arbitrate and interpret. The rate of scientific progress is determined by the interplay of such factors.

Problems that presently admit no speedy or tidy resolution will be addressed with all the energy and zeal we can command. In its first 90 years, NIH has added enormously to man's store of knowledge and has measurably enriched the nation's health. There is every reason to believe that when *Public Health Reports* celebrates its 200th anniversary, a future director of the National Institutes of Health will look back with pride on another century of outstanding progress.

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The National Institute of Health was established in 1930 and became the National Institutes of Health in 1948. Following are the years in which the Institutes and the National Library of Medicine were established.

National Cancer Institute	1938
National Heart, Lung, and Blood Institute	1948
National Institute of Dental Research	1948
National Institute of Arthritis, Metabolism and Digestive Diseases	1950
National Institute of Neurological and Communicative Disorders and Stroke	1950
National Institute of Allergy and Infectious Diseases	1955
National Library of Medicine	1956
National Institute of Child Health and Human Development	1962
National Institute of General Medical Sciences	1962
National Eye Institute	1968
National Institute of Environmental Health Sciences	1969
National Institute on Aging	1974

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**FRIDAY, DECEMBER 22, 1978**  
**PART VI**



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**DEPARTMENT OF  
HEALTH,  
EDUCATION, AND  
WELFARE**

**National Institutes of  
Health**

■

**RECOMBINANT DNA  
RESEARCH**

**Revised Guidelines**

**Revised  
Guidelines  
for  
Recombinant  
DNA  
Research**



60080

## NOTICES

[4110-08-M]

DEPARTMENT OF HEALTH,  
EDUCATION, AND WELFARE

National Institutes of Health

## RECOMBINANT DNA RESEARCH

## Revised Guidelines

I am announcing today several actions affecting the conduct of recombinant DNA research in this country.

In taking these steps, I have been guided by my responsibility to allow the maximum freedom of scientific inquiry consistent with the protection of the public health and the environment and with respect for the important ethical concerns surrounding genetic research in general.

The research techniques used to produce recombinant molecules of deoxyribonucleic acid, the complex chemical that codes genetic information for all living cells, hold great promise for significantly advancing our understanding of fundamental biological processes. Moreover, this research may also hold potential for the commercial production of needed biological materials and agricultural products.

From the pioneering days of this research, many of this nation's leading scientists expressed concern that the insertion of foreign genes into microorganisms could carry the potential for harm by yielding new disease-producing organisms. Although no harm has resulted from recombinant DNA research to date, there has been widespread uncertainty as to the degree of risk involved.

We must always recognize that scientific knowledge is not immutable; it is constantly changing as research generates additional information and understanding. Public policy in the field of science must therefore be flexible—to allow change as knowledge and understanding increase. The requirements that we impose must constantly be revised and updated to reflect new knowledge. Today the experience and insights that we have gained provide the basis for relaxing some of the restrictions the National Institutes of Health first imposed in 1976 on recombinant DNA research it funds.

The actions I am announcing today strive to allow the greatest freedom of scientific inquiry possible. At the same time, they provide the protections necessary to safeguard the public health and environment and also provide the opportunity for those concerned to raise any ethical issues posed by recombinant DNA research.

Specifically, I am today:

- Approving final guidelines prepared by the National Institutes of Health that significantly revise the

safety requirements for conducting recombinant DNA research;

- Taking immediate steps to require that research conducted by private companies complies with the NIH guidelines, primarily through use of the regulatory authority of the Food and Drug Administration (at Appendix A);

- Requesting the Environmental Protection Agency to review its authority and to take all action it can to require compliance with the NIH guidelines by companies that carry out DNA research but whose products are not regulated by the Food and Drug Administration;

- Directing NIH to increase its research designed to determine the extent of risk associated with recombinant DNA research (at Appendix B);

- Broadening substantially the public representation on the HEW advisory committee that will assist NIH in administering the revised guidelines;

- Increasing significantly public access to information about recombinant DNA research activities and increasing public participation in the administration of the guidelines in local communities.

## REVISED GUIDELINES

The revised final guidelines that NIH has developed and that I am approving today set new directions for regulation of future recombinant DNA research. These final guidelines retain much of the guidelines that NIH published in proposed form last July. But NIH has made many revisions based on public comment and on the review conducted by a Departmental committee. The Director, NIH, has prepared a Decision Document responding to the public comments and explaining the reasons for the revision.

The final guidelines relax some of the restrictions under which recombinant DNA research has been conducted since 1976, and at the same time increase the role of the public in approving and monitoring recombinant DNA experiments.

In particular, these final guidelines relax in two major respects the guidelines that were placed in effect in 1976.

- *The revisions exempt altogether five categories of experiments from the guidelines' restrictions.* NIH has concluded that these experiments present no known health risk. Approximately one-third of research covered under the existing guidelines would be exempted under the revised standards.

The revised guidelines continue to ban all six categories of potentially hazardous research that the 1976 guidelines prohibited. They will now, however, permit the Director of NIH to grant—following public notice and

comment—case-by-case exceptions to these prohibitions with appropriate safeguards.

- *The revised guidelines will ease restrictions on other permissible experiments.* Depending on the potential risk of an experiment, both the 1976 guidelines and today's revised guidelines require a researcher to comply with one of four levels of protective laboratory procedures and one of three levels of restrictions on the type of organism that may be used in the research. The revised guidelines assign almost all categories of research physical containment and/or biological containment levels at least one step lower than in the 1976 guidelines. Since the likelihood of harm now appears more remote than was once anticipated, the scientific community has now concluded that this downgrading is appropriate. The four levels of physical containment and three levels of "biological containment"—the use of weakened organisms that cannot survive outside the laboratory—set by the 1976 guidelines would remain the same.

Based on the review and public hearing conducted by a Departmental committee, the guidelines have been significantly rewritten from the July version to increase public participation at both the local and national level:

- *Twenty percent of the members of local Institutional Biosafety Committees (IBC's) must represent the general public, and have no connection to the institution.* The 1976 guidelines had no such requirements for public participation.

- *Important records must be made public.* The bulk of IBC records must be made available to the public and problems, violations, illnesses and accidents must be reported to NIH.

- *At the national level, major actions cannot be taken without advice of the Recombinant DNA Advisory Committee (RAC) with public and Federal agency comment.* Major actions include decisions to approve on a case-by-case basis experiments that are generally prohibited, to exempt additional categories of research from the guidelines, to permit the insertion of genes in new types of bacteria, and to approve changes in the guidelines themselves.

Finally, today's revised guidelines provide more explicit guidance both for local institutions and for NIH to follow in implementing the guidelines.

- *Institutions must develop emergency plans covering accidental spills and personnel contamination; health surveillance programs for projects needing such safeguards; and training programs for IBC members, researchers, and other laboratory staff.*

- *Under the revised guidelines, the NIH Director cannot approve pro-*



## NOTICES

60081

posed actions unless he determines that they present no significant risk to health or the environment.

## GUIDELINE COVERAGE

The revised guidelines apply to *all* recombinant DNA research conducted at any institution which receives NIH funds for recombinant DNA research. At these institutions, even research conducted without NIH support must comply with the guidelines. Other research agencies of the Federal government have assured us that they will require compliance with the NIH guidelines for all recombinant DNA research that they conduct or support.

We are also taking action to assure that the guidelines apply, to the greatest extent possible, to research conducted in the private sector.

● At my direction, the Food and Drug Administration is today announcing its intent to propose than any recombinant DNA research submitted to satisfy FDA's regulatory requirements must have been conducted in compliance with the NIH guidelines.

● I have also written to Douglas Costle, the Administrator of the Environmental Protection Agency (EPA) and asked him to review EPA's regulatory authority to determine whether EPA can regulate recombinant DNA research conducted privately that is not submitted to the FDA. I have asked him to take all action he can.

If both FDA and EPA act to regulate privately conducted recombinant DNA research, virtually all recombinant DNA research in this country would be brought under the requirements of the revised guidelines.

## BROADENED COMMITTEE MEMBERSHIP

I will announce shortly the names of 14 new members of HEW's recombinant DNA Advisory Committee. In addition to scientists who are experts in molecular biology and other disciplines, the Committee will be expanded to include persons knowledgeable in a wide variety of fields such as law, public policy, ethics, the environment and public health. The Committee will serve as the principal advisory body to the Director of NIH and to the Secretary of HEW on recombinant DNA policy.

## INCREASED RISK ASSESSMENT RESEARCH

While our knowledge about the risks of recombinant DNA has increased dramatically, much remains unknown. The scientific community must continue to assess the extent of the risks posed by recombinant DNA research. I am therefore directing the Assistant Secretary for Health and the Director of the National Institutes of Health to formulate a plan for carrying out a balanced program of additional risk

assessment experiments. In my view, the more risk assessment experiments NIH conducts or supports, the better we can judge whether the guidelines—and actions taken under them—afford appropriate protection for health and the environment.

Today's action represents the culmination of a long and thorough process that has sought at each step to balance the important concerns involved in recombinant DNA research. The National Institutes of Health in 1976 published guidelines to govern research which it funds.

The 1976 guidelines:

● Prohibited six categories of recombinant DNA experiments which experts felt posed significant hazards.

● Defined degrees of physical and biological containment necessary to prevent recombinant DNA organisms from escaping into the environment and surviving.

● Described permissible categories of recombinant DNA research and assigned levels of physical and biological containment for each.

● Described specific roles and responsibilities for principal investigators, research institutions, institutional biohazard committees, and the NIH.

Since issuance of the 1976 guidelines, recombinant DNA techniques have become much more widely used in research, and more has been learned about the limits of potential risks in using this technology.

In light of this new knowledge, the Director, NIH, on July 28, 1978 proposed substantial modification and relaxation of the guidelines. At that time, I named a Departmental review committee consisting of Peter Libassi, the Department's General Counsel, as Chairperson; Dr. Donald Fredrickson, the Director of NIH, as Vice Chairperson; Dr. Julius Richmond, Assistant Secretary for Health; and Dr. Henry Aaron, then Assistant Secretary for Planning and Evaluation. I asked the Committee to examine the proposed guidelines and to hold a public hearing on the guidelines.

In reviewing the guidelines, the committee solicited and heard comments from representatives of environmental groups, unions, pharmaceutical companies, institutional biosafety committees and Congressional staff members. The committee reviewed more than 170 letters from the public commenting on the revisions. The committee played a vital role in the process which led to the revised guidelines and unanimously recommended that the revised guidelines be approved.

These revised guidelines provide for a flexible, open system that can accommodate new scientific information that may warrant change, either to relax or to increase safety requirements.

I applaud all who have labored to develop these guidelines: The scientific community, the public, and workers at the Federal, State and local levels. This research holds promise for adding to our understanding about basic biological processes. These guidelines should permit that promise to be realized without presenting any significant risk to public health or the environment.

Dated: December 15, 1978.

JOSEPH A. CALIFANO, Jr.,  
Secretary.

## APPENDIX A

THE SECRETARY OF HEALTH,  
EDUCATION, AND WELFARE,  
Washington, D.C. 20201.

DECEMBER 15, 1978.

MEMORANDUM TO: Commissioner of Food and Drugs, Director, National Institutes of Health.

THROUGH: Assistant Secretary for Health.

SUBJECT: FDA Requirements for Compliance with the NIH Guidelines for Recombinant DNA Research.

With my approval and that of the Assistant Secretary for Health, the Director of the National Institutes of Health is issuing today revised Guidelines for Recombinant DNA Research.

These Guidelines set down requirements for all recombinant DNA research either conducted by NIH or conducted by institutions receiving NIH funds for recombinant DNA research. Other Federal agencies funding recombinant DNA research have agreed to require recipients of their funds to comply with these Guidelines as well.

To the maximum extent possible, we should extend the coverage of the NIH Guidelines to recombinant DNA research carried out in the private sector, with appropriate protection for proprietary and patent rights.

As we discussed, the pharmaceutical industry does most of the recombinant DNA research that is carried out privately in this country. Accordingly, the Food and Drug Administration is issuing today a Notice of Intent to propose regulations. These proposed regulations would require that all recombinant DNA research submitted to the FDA to satisfy the FDA's regulatory requirements be carried out in compliance with the Guidelines. This requirement should bring under the Guidelines the vast majority of recombinant DNA research conducted in this country by the private sector. If FDA does adopt such regulations, there must be close cooperation between NIH and FDA in implementing them. With the Commissioner of Food and Drug taking the lead, you should prepare a plan of action on the steps necessary to apply the Guidelines to the private sector.

Please submit a memorandum describing your proposed plan of action at the time you submit proposed regulations.

JOSEPH A. CALIFANO, Jr.



APPENDIX B  
THE SECRETARY OF HEALTH,  
EDUCATION, AND WELFARE,  
Washington, D.C. 20201.

DECEMBER 15, 1978.

MEMORANDUM TO: Assistant Secretary  
for Health, Director, National Institutes,  
National Institutes of Health.

SUBJECT: Assessing the Risk of Recombinant  
DNA Research.

With the issuance today of revised Guidelines for recombinant DNA research, the responsibility of the National Institutes of Health to conduct and support experiments designed to determine the risks of recombinant DNA research becomes even more important than it has been in the past. The revised Guidelines now require a finding by the Director of NIH that each proposed action under the Guidelines "presents no significant risk to health or the environment." It is critical that these judgments, to the maximum extent possible, be based on the firm foundation of documented research that is subject to peer review.

Experience and knowledge gained from the broad range of recombinant DNA research already underway will provide much information for assessing risks. But in many areas special research and careful attention will be needed. To discharge our responsibility to assess risk before certain research is conducted on a wide-spread basis, NIH should formulate a plan for carrying out a balanced program of more such risk-assessment experiments either at NIH directly or under NIH-supported grants or contracts. In my view, the more risk assessment experiments NIH carries out, the better we will be able to judge whether the Guidelines—and actions taken under them—afford appropriate protection for health and the environment.

Your overall plan to conduct risk assessment experiments should be published for public comment and presented for review to the Recombinant DNA Advisory Committee annually. The first such plan should be ready for publication and submission to the Advisory Committee by March 30, 1979.

JOSEPH A. CALIFANO, Jr.

NOTICE OF RELEASE OF REVISED NIH  
GUIDELINES FOR RECOMBINANT DNA  
RESEARCH

Today, the Director, National Institutes of Health, with the approval of the Assistant Secretary for Health and the Secretary of Health, Education, and Welfare, is authorizing the release of revised *NIH Guidelines for Research Involving Recombinant DNA Molecules*. The *Guidelines* and a *Decision* of the NIH Director to issue the revised guidelines are published below.

Dated: December 15, 1978.

DONALD S. FREDRICKSON,  
Director,  
National Institutes of Health.

DECISION OF THE DIRECTOR, NATIONAL  
INSTITUTES OF HEALTH, TO ISSUE RE-  
VISED GUIDELINES FOR RECOMBINANT  
DNA RESEARCH

DECEMBER 1978.

CONTENTS

I. Scope of the Guidelines.

General Applicability.  
Prohibitions and Exemptions—General  
comments.  
Prohibitions—Specific Comments.  
Exemptions—Specific Comments.  
II. Containment.  
Physical Containment.  
Shipment.  
Biological Containment.  
Flexibility in Choosing Physical and Bio-  
logical Containment Levels.  
III. Containment Guidelines for Covered  
Experiments.  
General Considerations.  
Risk Assessment.  
Specific Concerns.  
IV. Roles and Responsibilities.  
Of the Institution (General).  
Of the Institution (Special).  
Of NIH (General).  
Of NIH (Specific).  
V. Footnotes and References.  
Appendix A (Director's Decision concern-  
ing Appendix A of the Guidelines).  
Appendix B (Director's Decision concern-  
ing Appendix B of the Guidelines).

APPENDICES

I. Environmental Impact Assessment.  
II. Federal Interagency Advisory Commit-  
tee (list of members).  
III. Exchange of letters between Senators  
and Secretary Califano.

I. SCOPE OF THE GUIDELINES

A number of commentators at the September 15 hearing and correspondents addressed issues concerning the scope of the Guidelines. Views were expressed for an against exempting experiments from the Guidelines even though some argued that the risk was minimal or nonexistent. Specific issues that were raised are discussed below.

GENERAL APPLICABILITY

Several commentators spoke to the scope of the applicability of the Guidelines. Some questioned the right of NIH to apply the Guidelines to investigations not supported by NIH at an institution that receives some NIH funding for recombinant DNA research. Others, however, urged that the scope be broadened to include all institutions receiving NIH or, indeed, DHEW funding for whatever purpose.

I addressed these concerns in my Decision accompanying the proposed revision published in the FEDERAL REGISTER on July 28, 1978. I noted that partial adherence to the Guidelines within an institution would defeat the purpose of extending maximal protection to the community. Thus, it would be inconsistent for NIH to provide funds for recombinant DNA activities to an institution that did not meet the standards of the Guidelines in all of its recombinant DNA research, regardless of the source of funding. This principle is sound and NIH has the authority to apply it.

Some commentators took exception to the statement in the section on General Applicability that once certain research is approved at the local level, it may proceed. Several corre-

spondents pointed out that the language conveys the sense that all recombinant DNA research can proceed solely on the basis of local approval. This is not the case and this section does not, in fact, deal appropriately with the matter. Accordingly, the topic has been deleted from the Applicability section and dealt with extensively in part IV of the Guidelines and in the Administrative Practices Supplement.

Another commentator urged that the requirements of the Guidelines be extended to NIH-supported research in foreign countries. The proposed revised Guidelines (PRG) state that the Guidelines are applicable, but if the host country has rules for the conduct of recombinant DNA projects, then a certificate of compliance with those rules may be submitted to NIH in lieu of compliance with the NIH Guidelines, so long as the safety practices of the two are reasonably consistent. Of course, in countries with no guidelines, the NIH Guidelines must apply to NIH-supported research.

PROHIBITIONS AND EXEMPTIONS—  
GENERAL COMMENTS

There were a large number of comments on prohibitions, exceptions to prohibitions, and exemptions from the Guidelines. There was some confusion on the difference between exceptions and exemptions. Experiments excepted from the prohibitions are assigned appropriate containment levels and thus must be conducted in compliance with the Guidelines. For experiments under the exemptions (and not affected by prohibitions), the Guidelines do not apply at all.

Several of the commentators spoke to one or more of the criteria used for exempting experiments from the Guidelines. Some said that the criterion for granting exemptions should be safety and not whether DNA exchange occurs in nature. This issue is discussed in the Environmental Impact Assessment accompanying the revised Guidelines in the FEDERAL REGISTER of July 28, 1978.

It was noted there that, according to some commentators, safety rather than "novelty" should be the criterion for exclusion. That is, any recombinant molecule that poses a potential threat to the public health or the environment should be covered by the Guidelines regardless of whether the molecule is a novel one. An opposing view, expressed by other commentators, was that a proper criterion should be whether the potential hazard of the recombinant molecule would differ significantly from the biohazard posed by a molecule already found in nature or from a biohazard that can be successfully handled by conventional methods. It proved impossible to reconcile these differences of opinion in the definition itself, and



so the Exemptions sections was developed.

In my view, the criteria given in the exemptions and prohibitions sections of the PRG defining recombinations similar to natural events are both conservative and reasonable. It should be noted that the wording of prohibition I-D-5, "that are not known to acquire it naturally," is identical to that of the original 1976 Guidelines.

#### PROHIBITIONS—SPECIFIC COMMENTS

Several commentators requested clarification of prohibition I-D-2 concerning the deliberate formation of potent toxins. Was it intended to cover only toxins for vertebrates or those for all species? A commentator noted that fungi produce antibiotics that are potent toxins for bacteria. It is not the intent of this prohibition to cover such toxins but only potent toxins for vertebrates. Accordingly, new language makes it clear that "potent toxins" refers specifically to vertebrates.

A number of commentators from the agricultural community urged that mechanisms be set in place for waiver of prohibition I-D-4, which bans deliberate release into the environment of any organism containing recombinant DNA. Recognizing the need expressed by these commentators for more definitive standards for allowing exceptions, I will refer the matter to the Recombinant Advisory Committee (RAC) for its consideration. Indeed, in response to several suggestions from commentators, the RAC will be asked to address conditions under which exceptions to various prohibited categories of experiments may be granted.

Another commentator urged that for waiver of the prohibition on deliberate release into the environment, the Guidelines explicitly require compliance with the National Environmental Policy Act (NEPA) and any additional safeguards to be stipulated by EPA. Others urged that full Environmental Impact Statements be filed on most exceptions to the prohibitions. As I noted in my Decision accompanying the PRG on July 28, 1978, all waiver decisions will include a careful consideration of the potential environmental impact. Some decisions may be accompanied by a formal assessment or statement—a determination, however, that can only be made on a case-by-case basis. In the new procedures for the Federal agencies under the Guidelines, all agencies represented on the Federal Interagency Committee, including EPA and OSHA, will have nonvoting members on the RAC, and will thus have opportunity to participate in all the RAC's deliberations. In addition, the Federal Interagency Committee may be convened to discuss issues its members believe are important prior to the granting of any

waiver. Exceptions to prohibitions also fall under the procedure described in Section IV-E-1-b-(1) of the Guidelines that involves at least 30 days of public comment.

The standard for exceptions to prohibitions in the Guidelines was a source of much comment. Some commentators believe that the standard should be "no significant risk and a clear social benefit to be realized." Others urged that exception to the prohibitions be justified only to permit special risk-assessment experiments. I believe that Section IV-E-1-b sets the appropriate standard at this time. This is particularly so in light of the new procedural protections described in part IV requiring public and Federal agency participation in such decisions.

There were a number of comments from the private sector concerning the prohibition on large-scale experiments (I-D-6). They noted that the necessity for conducting scale-up experiments (greater than 10-liter volumes) is imminent, and that, in their view, such experiments present no unusual hazards. I recognize the need for conducting experiments with more than 10 liters of culture and the extensive experience of industry in dealing with larger volumes. The criteria set forth in the Guidelines make the prohibition inapplicable when the recombinant DNAs are rigorously characterized and free of harmful DNA sequences. An exception to the prohibition may also be granted [see Guidelines, Section IV-E-1-b-(1)-(e)] and the RAC will begin to consider specific standards for exceptions.

#### EXEMPTIONS—SPECIFIC COMMENTS

In the PRG all of the prohibitions overrode the exemptions. There were suggestions that certain prohibitions not apply to the exemptions. It was recommended, for example, that the prohibitions relating to the deliberate release of recombinants into the environment and the deliberate transfer of drug resistance not apply to exempt experiments. In my view these prohibitions must continue to apply for the present.

It was also argued that the prohibition on large-scale experiments should not apply to exempt experiments. This prohibition, indeed, is different from the other five, as is explicitly noted in the 1976 Guidelines. In the PRG the language was tightened: "recombinant DNAs known to make harmful products" was changed to "unless the recombinant DNAs are rigorously characterized and are shown to be free of harmful genes." For experiments in the exempt category that call for more than 10 liters of culture, it seems unnecessary to have the recombinant DNAs meet these criteria. Therefore, a

fixed prohibition, unduly restrictive in these cases, no longer applies, and experiments which meet the criteria of the exemptions may be conducted in volumes of over 10 liters. The first five prohibitions continue to apply to all experiments and override the exemptions.

A correspondent stated that the inclusion of specific exemptions in the Guidelines is premature. It was recommended that exemptions be granted instead on a case-by-case basis after risk-assessment, NEPA compliance, public participation, and a finding based on experimental data that the exemption presents no significant risk to health or the environment. In my view the five classes of exemption listed in the PRG, as discussed in the accompanying Decision Document and Environmental Impact Assessment, are warranted. It is a view shared by the RAC and many commentators throughout this long period of proposed Guideline revision. All of the participants and observers concerned with the Guidelines will benefit from disengagement of the least potentially hazardous use of recombinant DNA techniques, so that attention may be focused on the areas still encompassed by the Guidelines.

A witness at the September 15 hearing objected to exemption of experiments involving naked DNA, maintaining that the Rowe-Martin experiment showed that the ingestion of naked polyoma DNA by mice resulted in infection. This is incorrect. In that experiment the DNA caused infection in mice only when injected, and then with much reduced ability as compared with the whole virus. It is a common experience that naked DNA molecules are fragile and difficult to retain intact in the laboratory. Ingested DNA would be destroyed in the alimentary tract by stomach acid and the various enzymes that degrade DNA. The one route whereby naked DNA molecules might be hazardous is accidental injection, as into a laboratory worker. The same could be said for many of the chemicals used in experiments. For this reason, the use of hypodermic needles in laboratory procedures is avoided whenever possible. Their use is specifically discouraged in the section of the Guidelines on Containment. Further, Footnote 5 has now been expanded to recommend inactivation of DNA before disposal, and specifically refers to the Laboratory Safety Monograph as a source of advice on acceptable methods.

A commentator on behalf of the RAC's Working Group on Prokaryotic Host-Vectors Other than *E. Coli* K-12 proposed modification of Exemption I-E-3. He provided the following justification: "Addition of the proposed clause [or which have been trans-



ferred to another host by known physiologic means<sup>1</sup> will exempt the following types of experiments:

"An *E. coli* strain is constructed in which a chromosomal gene of *E. coli* has been enzymatically joined to plasmid DNA; this plasmid is then transferred by conjugation into another bacterial host that is not on the Director's List of bacteria that exchange with *E. coli*.

"It seems logical that this experiment should be exempt, because it involves natural genetic exchange between two organisms both of which are exempt. The *E. coli* donor is exempt because it represents a gene combination that could easily arise by natural means. As the transfer can also occur naturally, the same statement applies also to the second host carrying the plasmid.

"If unidirectional plasmid transfer had been accepted as an adequate criterion for inclusion on the Director's List, the strain would be automatically exempt. The reason for not accepting this criterion was that some doubts had been expressed as to whether unidirectional plasmid transfer automatically implied bidirectional transfer of chromosomal genes. However, in the present case, the ability to construct the desired recombinant is *de facto* evidence that it could arise by natural means.

"A specific proposal was submitted to RAC \*\*\* to splice an *E. coli* suppressor into an *E. coli* transposon, then move the resulting combination into *Myxococcus* by P1 transduction. This strategy will allow the isolation of suppressible mutants of *myxococcus* and its phages, which will greatly expedite genetic studies of development and motility in that organism."

The change as proposed by the commentator is warranted in my view, and has been made, with minor rewording for clarity.

There were many comments concerning the list of exchangers in Appendix A to be exempt from the Guidelines under exemption I-E-4.

Many commentators urged more explicit standards for inclusion on the list. As discussed in detail in the section of this document dealing with Appendix A, the criteria for inclusion on the list have been tightened and made more explicit, reducing the list considerably and thus exempting fewer experiments from the Guidelines.

## II. CONTAINMENT

The object of the containment provisions of the proposed revised Guidelines is to ensure that experimental DNA recombination will have no ill effects on the researchers, the general public, or the environment. Public comments on part II of the Guidelines and on the Laboratory Safety Mono-

graph were generally supportive. However, a number of pertinent issues relating to physical and biological containment were raised in correspondence and at the public hearing held on September 15, 1978. They deserve consideration and are addressed below.

### PHYSICAL CONTAINMENT

#### *Effectiveness of Physical Containment*

One commentator observed that laboratories cannot provide foolproof containment of dangerous organisms and that a biohazard outbreak can rapidly spread to virtually any neighborhood on earth. He cited the recent laboratory accident in England attributed to the escape of a smallpox virus through a faulty filter. NIH agrees that when known hazardous agents are dealt with, the risk of a laboratory-acquired infection cannot be totally eliminated. I believe, however, that adherence to the Guidelines provides ample protection for laboratory personnel, the public, and the environment. Even if an organism should escape from the laboratory, the mutational changes underlying "biological containment" would greatly decrease the probability that it would survive in the environment. The recent incident in England involves an extraordinarily hardy, resistant, and virulent organism to which man is very susceptible—one that is hardly comparable to weakened strains of *E. coli* generally used in recombinant DNA research or to the new host-vector (HV) systems now under consideration.

#### *Laboratory Practices*

A correspondent noted that persons on antibiotics or immunosuppressive drugs, or those with open lacerations or chronic digestive abnormalities, are not prohibited from entering the laboratory under any of the physical containment levels. In response, it should be pointed out that the *Laboratory Safety Monograph (LSM)*, page 204, provides that "laboratory workers who are undergoing treatment with steroids, immunosuppressive drugs or antibiotics, or are suffering from colitis, ileitis, active chronic diarrhea, or other gastrointestinal disorders, should have a medical evaluation to determine whether they should be engaged in research with potentially hazardous organisms during the time of their illness." Reference to this now appears in Section IV-D-1-h, which also mandates that the institution shall provide health surveillance of laboratory personnel.

Several commentators noted that absence of specific guidance for the rodent and insect control programs required in Section II-B-1-a-(9), II-B-2-a-(12), II-B-3-a-(12), II-B-4-a-(16). The large variety of situations and animal involved makes precise speci-

cations impractical. It is the intent of the Guidelines, however, that adequate attention be paid to this problem, and further guidance will be provided in the next edition of the LSM.

#### *Emergency Procedures*

One commentator urged that the Guidelines include specifications for cleanup procedures to be followed in the event of a spill or accidental release of organisms into the environment. A witness recommends that for prompt and adequate response to emergencies, a team of experts from NIH and CDC be formed, and that their names and telephone numbers be published for easy access. Emergency procedures are currently detailed in the LSM, pp. 194-195. These will be expanded in the next edition of the monograph to provide for an NIH-CDC emergency consultation and response program to assist institutions in managing serious accidents. Twenty-four-hour telephone coverage will afford an immediate response capability.

One correspondent recommended that all bacteria used in recombinant DNA experiments be tagged so that their spread, in the event of an accident, could be detected in the environment. A general requirement to this effect is not now practicable. It should be noted, however, that in many cases bacteria are tagged to permit identification.

A correspondent raised the prospect that P2 and P3 containment facilities could be compromised by an earthquake. Most institutions have emergency plans for dealing with natural disasters. Selected references are cited in the LSM. If necessary, NIH and CDC are available to provide direct assistance in the management of specific emergency situations. Moreover, institutions in areas subject to natural disasters such as earthquake must generally conform to building code requirements that are designed to minimize the effects of such disasters.

#### *Issues Related to Specific Containment Levels*

A number of additional comments were received from public commentators relating to the proposed actions at specific levels of physical containment.

One correspondent said that the new P1 and P2 containment conditions are not significantly different, and that the difference between P1 and P2 should be approximately the same as that between HV1 and HV2. He objected strongly to the escalation of the P1 and P2 containment rules.

NIH believes that the differences between the two levels of containment are significant. For example, P2 requires use of biological safety cabinets to contain aerosol-producing equipment, use of the universal biohazard



sign, and use of gowns, coats, and uniforms. It limits entry into a laboratory to those who have been specifically informed advised of the nature of the research being conducted.

In response to a witness who averred that P1 actually represents no containment, it can be noted that P1 is the equivalent of the physical-containment level used in medical microbiological and hospital diagnostic laboratories throughout the world for handling infectious organisms. Indeed, it was suggested that a need exists for an even lower level of physical containment than P1 (for organisms considered of minimal risk). I do not believe it prudent, however, to permit a lower level of containment for experiments covered by the Guidelines.

In the *Decision of the Director* published with the NIH-proposed revised Guidelines on July 28, 1978, I indicated that mouth-pipetting would no longer be permitted in P1 containment. Since it is already prohibited in P2 through P4 containment, this would ban the use of mouth-pipetting for any experiment covered by the Guidelines. One commentator feels that mouth-pipetting should not be prohibited under P2 conditions and should definitely be allowed under P1 containment because of its superior efficiency. The banning of mouth-pipetting at the P1 level, however is in accord with the advice of safety experts; the present availability of excellent mechanical devices for pipetting makes the alternative, in my opinion, a practicable one.

A correspondent suggested that use of biohazard signs at the P2 level of containment should be discontinued: "They should be reserved for demonstrated biological hazards. There is a real danger that overuse of these signs in cases where workers know they do not apply will lead to the ignoring of all biohazard signs." While I recognize the concern expressed, I feel it prudent to require the universal sign at the P2 level when recombinant DNA materials are being handled.

For the P3 level of containment, one commentator suggested that an autoclave be within the controlled laboratory area, if not the laboratory itself, rather than merely in the same building. Another commentator makes a similar point for the P2 level. This issue was raised in comments on the revision of the Guidelines proposed by the Recombinant DNA Advisory Committee (PRG-RAC, *FEDERAL REGISTER*, September 27, 1977). As stated in my *Decision* (*FEDERAL REGISTER*, July 28, 1978), "... an absolute requirement that the autoclave must be within the controlled area is not considered appropriate, since contaminated material can be safely transported. Such a requirement would exclude the use of

autoclaves in waste-staging areas that have been conveniently sited to support an entire facility."

A commentator questions for entrance of children into P3 facilities. After considering this issue, I have decided to (1) retain the stipulation that persons under 18 years of age shall not enter a P4 facility, (2) raise the age limit for entry to P3 laboratories from 12 to 16 years of age, and (3) eliminate the age stipulation for P2 laboratories.

A recommendation that the use of a separate centrifuge room or cubicle be provided in a P3 facility to contain spills occasioned by rotor failure has not been accepted. All rooms in the P3 facility must be capable of being sealed to facilitate space decontamination. Modern centrifuges do not present the potential hazard associated with earlier models. Rotor design, operation requirements, the design integrity of the centrifuge well, and the availability of sealed centrifuge cups adequately control the aerosol hazard associated with centrifuging.

Other concerns relating to the P3 level of physical containment have been considered:

- Section II-B-3-c-(7), dealing with ventilation, has been completely rewritten to clarify the intent to permit recirculation of HEPA-filtered exhaust air.

- Section II-B-3-c-(5), which requires that laboratory doors be self-closing, has been deleted. As a correspondent observes, the Guidelines should be worded in such a way as to make facility design compatible with Section II-B-3-a-(1) requiring laboratory doors to be closed while experiments are in progress has been retained.

- A recommendation that the Guidelines be revised to require that booties be worn at all times within the P3 laboratories has not been accepted.

For the P4 level of physical containment, one correspondent would have the Guidelines specifically require the use of gloves. In response, it can be noted that most P4 experiments use Class III cabinets, which are fitted with attached arm-length rubber gloves. As shown in Table II of the PRG-NIH, however, one can work in open-faced biological safety cabinets with augmented biological containment. In this case, the requirement for gloves has now been explicitly set forth by addition of text to Table II.

In response to commentators' suggestions and NIH review, other changes have been made in the Guidelines. For example:

- Sections II-B-1-a-(5), II-B-2-a-(5), and II-B-3-a-(5) have been changed to indicate that eating, drinking, smoking, and storage of foods are not permitted in the "laboratory area

in which recombinant DNA materials are handled."

- Sections II-B-2-a-(10) and II-B-3-a-(11) have been changed to mandate the posting of the universal biohazard sign on freezers and refrigerators "or other units" used to store organisms containing recombinant DNA molecules. In addition, the requirement for identifying storage units within the P4 facility with the universal biohazard sign has been included in Section II-B-4-a-(15).

- Additional language to clarify the use of the terms "sterilized" and "decontaminated" has been added to Sections II-B-1-a-(3), II-B-2-a-(3), II-B-3-a-(3), II-B-3-a-(8), II-B-4-a-(9), and II-B-4-a-(10).

- The requirement that the laboratory be kept neat and clean has been added to P1; it was already present at P2, P3, and P4.

- A new Section II-B-4-(18) has been added concerning vacuum outlets in the P4 facility.

#### SHIPMENT

New language to clarify the intent of Section II-C relating to shipment has been suggested by the Department of Transportation. This language has been incorporated (with minor modifications) into the Guidelines. The suggestion of one correspondent that certain clones be exempt from these requirements has not been accepted.

#### BIOLOGICAL CONTAINMENT

##### *Certification of Host-Vector Systems*

Most comments on the biological containment provisions of the proposed revised Guidelines related to development, review, and approval of host-vector (HV) systems other than *E. coli* K-12. In particular, commentators from the scientific community continue to urge development of such alternate systems. Thus, one correspondent wrote, "The anticipated potential of recombinant DNA in agriculture will be difficult, if not impossible, to realize with *E. coli* K-12 host-vector systems. Therefore, it is imperative that attention be given to the development and approval of alternate HV1 systems that may be useful in genetic engineering of plants and invertebrates." Another correspondent wrote, "While many of the regulations do not add to the safety of what are basically safe experiments, they do serve to inhibit the development of new and versatile vector systems \* \* \*. The redundant safety testing program is too onerous, time-consuming, and in our opinion, not scientifically justified."

While I agree that research based on other host-vector systems must proceed, I believe that certification of these systems should be approached conservatively. The new systems raise



ecological and biological issues that must be carefully and thoughtfully addressed. As one correspondent cautioned, "We must be very careful when, bolstered by our confidence in *E. coli* K-12 systems, we try to extrapolate to *B. subtilis*, yeast, etc." Two Working Groups of the RAC have recently met to consider alternate systems and to develop more precise and objective criteria for certification.\* Many problems, however, persist for setting general standards that could be applied to all organisms. I believe that the process of review and approval described in the Guidelines will allow for full and deliberate examination on a case-by-case basis of putative HV systems and of pertinent ecological and biological issues. This process will, of course, comply fully with NEPA.

In response to one correspondent's suggestion, text has been added to Section II-D-2-a further clarifying the roles of the NIH Director and ORDA in the process of certification.

#### *Data Required for Certification*

One correspondent suggested an expansion of Section II-D-2-b-(1), relating to data to be submitted for certification of HV1 systems other than *E. coli* K-12. Specifically, he would require a thorough discussion of the physiological properties of the organism, particularly those related to its reproduction and survival and the mechanisms by which it exchanges genetic information—not simply the range of organisms with which it exchanges. I believe these characteristics to be especially crucial in approval of new systems; accordingly, Section II-D-2-b-(1) has been amended to incorporate this suggestion.

#### *EK1 Systems*

One correspondent noted that most host components of EK1 systems used in recombinant DNA research have mutations in addition to those acquired during K-12's laboratory evolution that confer special nutritional requirements, cause recombinants to be defective, or otherwise diminish survival or reduce the likelihood for transmission of recombinant DNA. It has been suggested that use of such mutations should be encouraged. In my view, much of the value of the EK1 host is its flexibility, and it does not seem necessary to explicitly recommend certain strains of *E. coli* K-12 as EK1 strains. The investigator will generally choose the more readily transformable *E. coli* K-12 strains, and many of the characteristics that enhance transformability decrease survival. In addition, by suggesting the

use of certain mutations, we may shut off research on others which might prove even more useful and safe.

#### **FLEXIBILITY IN CHOOSING PHYSICAL AND BIOLOGICAL CONTAINMENT LEVELS**

One witness and one correspondent questioned the rationale for allowing alternate levels of physical and biological containment. The concept of "flexibility" is discussed at some length in the *Decision* document, *FEDERAL REGISTER*, July 28, 1978, pp. 33052-33053, and in the accompanying *Environmental Impact Assessment*, p. 33113. Moreover, the flexibility allowed in alternate P and HV levels is carefully explained in the text of the Guidelines, and the investigator must follow the explicit requirements set forth in part III of the Guidelines and Tables I and II.

#### **III. CONTAINMENT GUIDELINES FOR COVERED EXPERIMENTS**

##### **GENERAL CONSIDERATIONS**

Many of the commentators supported the levels of containment recommended for covered experiments. They concurred with the scientific arguments presented in the *Decision* document and *Environment Impact Assessment* (issued July 28, 1978) as a rationale for lowering containment levels. Some cited the reports of the Falmouth and Ascot risk-assessment meetings as confirmatory evidence, and reiterated that *E. coli* K-12 cannot be converted into an epidemic pathogen even by the introduction of additional genes from known pathogenic strains.

Many commented favorably on specific sections of the Guidelines, such as the lowered containment levels for viral DNA. Others supported the proposed containment levels for the cloning of primate DNA. One further stated that relaxation would permit major studies to be made in locating and mapping human genes. Another noted that the proposed revisions would permit the conduct of research with plants and plant-associated microorganisms and endorsed the changes based on the Workshop on Risk Assessment of Agricultural Pathogens.

A number of commentators, while generally supportive of the changes proposed, believed the Guidelines to be still too restrictive. Some urged that they either be dispensed with entirely or, in the opinion of one commentator, be replaced with the following sentence: "It would seem prudent to conduct work with organisms containing recombinant DNA under laboratory conditions appropriate to the degree of pathogenicity of the donor organisms."

I appreciate the thoughtfulness and care that have gone into the many letters. I also acknowledge a belief that the proposed revised Guidelines represent a conservative lowering of containment based on data and analysis discussed in detail in the *Decision* document and *Environmental Impact Assessment* of July 28, 1978.

On the other hand, there were commentators and witnesses who believed the lowering of containment levels in the proposed revised Guidelines was not justified. While there was a difference of emphasis in many of the comments, there appeared to be several major concerns. I shall consider each of these in turn.

● Commentators state that "much of the evidence [that NIH cites as a basis for lowering containment] has never been published or is available only in summary form." Also that "A great deal of weight has been placed on semi-authorized reports of discussions held at closed scientific meetings, attended by a small number of selected participants." They express concern that such action by NIH has prevented the wider scientific community from critical appraisal of the data. Various of these commentators state that the results of the Falmouth conference were published only two months before the proposed revision of the Guidelines was issued, that the proceedings of the Ascot conference have not been issued, and that the results of the Rowe-Martin risk-assessment experiments have not yet been published.

The extensive proceedings of the Falmouth meeting, held in June 1977, were published in the *Journal of Infectious Diseases* in May 1978. Publication in journal form usually involves a considerable delay, even after the edited manuscript, in this case constructed of transcripts of papers and discussions edited by participants, has been completed. The moderator of the Falmouth meeting, Dr. Sherwood Gorbach, Professor of Medicine and Microbiology, Tufts University School of Medicine, summarized the outcome of the meeting in a letter to me on July 17, 1977. (This letter was published as Appendix M to the October 1977 *Environmental Impact Statement*, and was also published along with letters from other participants in the *Recombinant DNA Technical Bulletin*, Volume 1, No. 1, Fall 1977.)

The report of the Ascot meeting was published as Appendix E to the *Environmental Impact Assessment (EIA)* in the *FEDERAL REGISTER* on July 28, 1978, pp. 33159-33167, and previously in the *FEDERAL REGISTER* on March 31, 1978, pp. 13748-13755. Its introduction says, "A draft of this report was sent to the members for comment and revi-

\*The Working Group on Prokaryotic Host-Vectors Other Than *E. coli* met on September 12, 1978; and the Working Group on Lower Eukaryote Host-Vector Systems met on September 16, 1978.



sion, and this final version is based on the replies of all the participants."

The report of the Virus Working Group, which considered the Ascot Report, was published as Appendix F to the EIA in the *FEDERAL REGISTER* July 28, 1978, pp. 33167-33174.

The 36 participants at the Falmouth meeting are listed in the report of the meeting (*Journal of Infectious Diseases*, Vol. 137, pp. 613-614, May 1978). Most of the participants were invited by the organizing (steering) committee for the meeting, and the members of that committee are listed on these pages. In addition to invited participants, others arrived uninvited and participated.

The participants and the reasons for holding the Ascot meeting are discussed in my Decision document (*FEDERAL REGISTER*, July 28, 1978, p. 33060) and in the EIA, p. 33159.

The participants in the Virus Working Group, which met on April 6-7, 1978, to review the report of the U.S.-EMBO Workshop, are described in the EIA. (*FEDERAL REGISTER*, July 28, 1978, p. 33167). This meeting was announced in advance in the *FEDERAL REGISTER* on March 17, 1978; it was entirely open and was attended by others than the participants.

The results of the Falmouth, Ascot, and Virus Working Group meetings were discussed at a number of meetings of the Recombinant DNA Advisory Committee (RAC), where they led to recommendations for changes in the Guidelines. All meetings of the RAC have been announced in advance in the *FEDERAL REGISTER*, have been open to the public, and have been attended by many nonmembers.

The NIH is sensitive to the need for all concerned to have access to the advisory deliberations contributing materially to the substance and use of these Guidelines. Ordinarily, such meetings will be open to the public and announced in advance in the *FEDERAL REGISTER*. We have become aware that publication in the *FEDERAL REGISTER* is not sufficient notice for many, and the *Recombinant DNA Technical Bulletin* and other media will be used whenever possible to supplement announcements of meetings and disseminate reports emanating from them. NIH will also continue its publication of all commentary, transcripts of hearings, and other materials relevant to the "public record" of deliberations on the subject of the Guidelines.

Commentators state that the absence of untoward events in five years of experiments with recombinant DNA is not a valid ground upon which to justify the lowering of containment levels.

There is some merit in this objection, but experience to date should contribute to the basis for revision of

the Guidelines. When organisms containing recombinant DNA began to be constructed in 1973, it seemed unlikely to most that hazardous organisms would be produced, yet no one knew for sure. No basis for certainty has yet arrived, but some of the fears have justifiably diminished. The results to date have revealed no major biological factor overlooked in the initial analysis that suggests the guidelines should be stricter than they are. Indeed, several separate lines of evidence indicate the probability of hazards to be even lower than originally thought. That no one has become ill is the least impressive of these. More important lines include the following:

1. Numerous analyses and newer data indicating the very low probability that *E. coli* K-12 will establish itself in the human intestinal tract, thus limiting escape of the organisms in numbers sufficient to infect other living things.

2. The now widely made observation that organisms containing recombinant DNA compete very poorly for survival as compared with organisms not containing recombinant DNA. This was an anticipated finding (see October 1977 Environmental Impact Statement) but has now been documented in various instances. It is true even under laboratory conditions designed to be optimal. Only when the growth medium for the *E. coli* cells containing recombinant DNA is specifically designed to impose selective pressure on the recombinant organisms do they outgrow "Natural" competitors. (Selective pressure could be imposed, for example, by the presence of an antibiotic to which the recombinant organisms are resistant but the natural competitors are sensitive.)

3. The repeated observation that genes of higher organisms, introduced into *E. coli* by shotgun experiments, are not generally expressed. Many of the concerns about possible hazards center on the ability of a host cell to synthesize a foreign protein that might be detrimental to an organism with which the host cell comes into contact.

One correspondent said that assigning a higher degree of containment to organisms that are phylogenetically closer to man is unjustified, with the possible exception of clones capable of harboring viral sequences. The correspondent noted that "even if the cloned DNA were highly homologous to human DNA, how is it envisioned that when carried in a bacterial host it would somehow be more dangerous to man than a non-homologous DNA?" The commentator went on to state that the "production of pharmacologically active agents will clearly not depend upon evolutionary similarity to man" and that in fact such prod-

ucts will likely be specified by lower organisms.

In responding, I must note that a primary concern in the original assignment of containment levels was the possibility that viruses capable of propagating in human tissues could contaminate the DNA. The concern is greatest when the DNA donors are primates or other mammals, and so, for these, higher containment levels are provided.

A secondary consideration involves the possibility that the recombinant DNA may itself transform the host. The likelihood of such DNA integrating into the human genome, and consequently undergoing replication and expression, is directly related to the extent of homology between the foreign and host DNAs.

Another reason for making distinctions on the basis of phylogenetic relatedness is that the more closely related the species, the more likely that polypeptide hormones or related proteins would be pharmacologically active.

A more extensive discussion of the issue of phylogenetic relatedness is given in the Environmental Impact Assessment (*FEDERAL REGISTER*, July 28, 1978, pp. 33102-33104). This matter lies in a crucial area of risk analysis and will undoubtedly continue to be subject of both further debate and improved understanding in the coming months.

Commentators discuss a number of scientific "fears where there remains reason for caution," including that the virulence of *E. coli* may be increased by recombinant DNA, that recombinant plasmids might be transferred to more virulent strains of bacteria, and that bacteria or viruses containing recombinant DNA could cause autoimmune disease.

In reply, I note that these issues are discussed extensively in the proceedings of the Falmouth Conference (*Journal of Infectious Diseases*, May 1978) and in the EIA of July 28, 1978 (*FEDERAL REGISTER*).

At the Falmouth conference, evidence was presented on the attempts to make *E. coli* K-12 pathogenic. Even the introduction of *Shigella* genes into *E. coli* by nonrecombinant DNA techniques failed to produce a pathogenic organism having any phenotype suggestive of *Shigella*. There was consensus of all participants at Falmouth that *E. coli* K-12, could not be converted into an epidemic pathogen by recombinant DNA techniques.

There are great safety differences between *E. coli* K-12, an attenuated laboratory strain, and wild-type *E. coli*, as discussed in the EIA.

For an EK2 host to be certified as such, "no more than 1 in 10<sup>4</sup> host cells should be able to perpetuate a cloned



DNA fragment under the specified nonpermissive laboratory conditions designed to represent the natural environment, either by survival of the original host or as a consequence of the transmission of the cloned DNA fragments."

A concern expressed by the commentators is that plasmids containing recombinant DNA might be transferred to other, wild-type organisms in the gut. Some appropriate risk-assessment studies concerning this possibility are being carried out. However, the Falmouth report and tests of EK2 host-vector systems present the following data to indicate that the probability of such transfer of the plasmids is extremely low:

1. H.W. Smith, looking specifically for transfer of a conjugative plasmid from *E. coli* K-12 to normal gut flora, could find no evidence that transfer occurred (Falmouth report, pages 655-660). For biological containment to be breached, transfer of a conjugative plasmid to *E. coli* K-12 would have to occur to be followed by transfer of the poorly mobilizable recombinant plasmid from *E. coli* K-12 to other organisms. (Conjugative plasmids themselves are not allowed to be used as vectors.)

2. Gene transfer *in vivo* greatly increases with colonization by both donor and recipient organisms, and colonization by *E. coli* K-12 in general and x1776 in particular is very rare.

3. Mobilization of the plasmids used in recombinant DNA experiments is extremely low, even under optimal *in vitro* conditions.

4. Transfer of the recombinant-containing vector would require a triparental mating *in vivo*, which even under the most favorable of *in vitro* conditions is not a high-frequency event. Such transfer has not been observed *in vivo*.

5. One commentator suggests that transduction might be an important mode of gene transfer. "Generalized transduction" by phage lambda does not occur. Generalized transduction by phage P1 is a low-frequency event (less than  $1/10^6$  infected organisms are transduced for a particular marker) under the very best of *in vitro* conditions.

Additional information on plasmid transfer may be found in the Environmental Impact Assessment (FEDERAL REGISTER, July 28, 1978, p. 33123) and the previous October 1977 Environmental Impact Statement, both of which consider the possibility of transfer of foreign DNA from *E. coli* K-12 as well as the ability of *E. coli* K-12 to survive and spread in nature. As noted in both these documents, the maximum probability for transmission of nonconjugative plasmid vectors from *E. coli* K-12 was estimated at "less

that 1 to 1016 K-12s surviving per day in the intestine of warm-blooded animals. The probability is even lower in sewers, sewage treatment plants, and waterways." The EIA further states that *E. coli* K-12 survives poorly and is outcompeted by wild-type enteric bacteria.

The concern expressed by the commentators about the possibility of autoimmune disease will only prove true if a series of events occurs. The very low probability of the establishment of *E. coli* K-12 containing recombinant DNA in the intestinal flora is discussed above. In addition, the inserted eukaryotic gene must be transcribed, translated, and transported to a place where it can induce an immune response. These steps are highly unlikely to occur.

#### RISK ASSESSMENT

NIH is supporting a number of risk-assessment activities. The Rowe-Martin polyoma experiments are discussed elsewhere in this document. In addition, intramural NIH scientists are collaborating with scientists from other institutions testing the virulence in mice of *E. coli* K-12 containing "shotgun clones" of recombinant DNA derived from other species.

A number of contractors of the National Institute of Allergy and Infectious Diseases are testing the biological containment capabilities of various derivatives of *E. coli* K-12. Some are testing the survival and capacity of plasmid and phage vectors to be transmitted to secondary bacterial hosts in the gastrointestinal tract of mice and man. Others are assessing these parameters in model sewage treatment systems and in situations simulating accidental spills and other types of accidental release of the organisms from experimental procedures.

In addition, investigators proposing systems to be certified by NIH as HV1 or HV2 must perform certain specified tests on these systems relevant to their survival and transmission properties. It is also anticipated in the event that investigators request exceptions to the prohibitions for specified clones, NIH will request substantial risk assessment experiments to be performed to evaluate claims of safety.

#### SPECIFIC CONCERNS

In addition to their general remarks about the experimental section of the Guidelines, many commentators raised questions about the containment levels set for specific experiments. Others suggested clarifying language for certain sections. I have taken all of these recommendations under consideration. In some instances I have concurred and the Guidelines reflect the change. In others I have decided not to act or have deferred actions pend-

ing further analysis and discussion by the Recombinant Advisory Committee. In all cases I have attempted to respond and to explain the decision.

#### Section III-A-1: Shotgun Experiments

Comments from respondents on this section of the Guidelines reflected diametrically opposed points of view. Some commentators questioned the rationale for lowering of containment levels for shotgun experiments.

Other correspondents took a different view and requested that NIH further reduce the containment level for shotgun experiments. One advanced the argument that "these pieces of DNA in *E. coli* cannot be more dangerous than their original source."

I have decided to retain those levels of physical and biological containment described in the proposed revised Guidelines. I believe the specified containment levels represent a prudent, albeit most conservative, response to the hypothetical hazards. Rationale for them is presented in the July 28, 1978, Decision document and Environmental Impact Assessment.

Risk analysis by NIH is continuing. One important area of analysis involves the appropriateness of higher containment levels for shotgun experiments, with the tremendous dilution of potentially harmful genes, in contrast to purified clones that have been "engineered" for efficient transcription and translation of DNA inserts.

#### Section III-A-1-a. Eukaryotic DNA Recombinants Including Primates, Other Mammals, and Birds

Twelve commentators, the largest number of comment on a single issue, wrote to express their views on the limitation of P2+EK2 under the proposed revised Guidelines for the cloning in *E. coli* K-12 of shotgun DNA from primates, other mammals, and birds. All requested that the option of P2+EK2 or P3+EK1 be offered.

One group argues that to restrict cloning of these classes of DNA to P2 + EK2 is inconsistent, since many viral genomes could be cloned at either P2 + EK2 or P3 + EK1. Other respondents pointed out that use of P3 + EK1 conditions would provide adequate containment and would permit the inclusion of lysogenic lambda systems, which cannot be employed in an EK2 system. One stated that propagating DNA fragments in EK1 host-vector systems permits a 5-10 times greater yield of DNA than in an EK2 system. "Thus the advantage of EK2 containment should be weighed against the necessity of handling much larger volumes of cells."

I referred this matter to the RAC at their October 30-31, 1978, meeting. The RAC advised that the phrase "or P3 + EK1" be added to Section III-A-1-a-(3) (i.e., for DNA from birds) and



## NOTICES

this has been done. For Sections III-A-1-a-(1) and III-A-1-a-(2) (DNA from mammals), the RAC recommended addition of the phrase "or P3 + EK1 with a non-mobilizable plasmid." Because the term "non-mobilizable plasmid" is not clearly defined, I am not accepting this recommendation at present, pending further review at the next RAC meeting.

**Section III-A-2-a. DNA From Virus of Eukaryotes Into *E. Coli* K-12**

There was considerable comment about various aspects of Section III-A-2-a, extending from general concerns about the reduction of containment levels from viral inserts to detailed and specific recommendations for clarification of certain phrases.

Several correspondents objected to the general relaxation of containment levels for the cloning of viruses. One stated that although the Ascot conference concluded that "cloning of the whole or any part of a viral genome must logically be less dangerous than working with the virus," his view is just the opposite. The arguments presented by this correspondent are (1) whole virus can elicit the production of antibodies, (2) whole virus with its protein coat is subject to a biological barrier which limits infection across species lines, and (3) whole virus is eliminated from the body after infection. In the view of this correspondent, all of these protective devices are subverted by cloning viral genes in a microorganism that may become established in the intestinal tract. He is also concerned that the Guidelines are not sufficiently stringent for cloning subgenomic DNA fragments of viruses. Another respondent indicated that belief that containment experiments involving animal-cell transforming viruses were substantially reduced, based on the supposed inefficiency of infection by naked DNA. She continued by stating that the decision to lower containment did not take into account the results of the Rowe-Martin risk-assessment experiments with polyoma DNA, which showed that naked polyoma DNA when injected into the bloodstream of mice caused a low-level infection.

The recommendations of the Ascot Workshop (Appendix E to the Environmental Impact Assessment), the subsequent Working Group review (Appendix F to the EIA), and the subsequent RAC review took into account the concerns of correspondents about viral containment, but nevertheless recommended lowered containment levels based on the conclusion that cloning of viruses or their fragments in *E. coli* could be no more dangerous than working with the intact virus. The containment levels were set accordingly. The three reasons cited

above as to why the cloned virus DNA might be more dangerous than the whole virus apply only to the first infected cell. The DNA would produce disease only if it became virus and spread; thus, the situation becomes the same as the usual virus infection. This possibility was thoroughly considered at Ascot, and is in the summary report of that meeting. Also, the existence of a subgenomic fragment precludes virus production and so effectively prevents the spread of infection.

The Rowe-Martin risk-assessment experiments (still in progress) are designed to compare the infectivity of a recombinant molecule containing polyoma DNA with that of nonrecombinant polyoma DNA and of whole polyoma virus. To date, there are no data available from these experiments which would lead me in any way to revise the judgements of the meetings cited above.

In response to the concern expressed about naked DNA, there is a significant difference in level of infectivity between naked DNA and whole virus particles; naked DNA is much less infectious than the virus. For additional discussion of naked DNA, see part I of this document.

A correspondent stated that there should be some definition as to whether a DNA virus is a transforming or nontransforming virus. To clarify this, a new footnote (37A) has been added to Section III-A-2-a-(1)-(b).

A correspondent pointed out that there are places in Section III-A-2-a where the word "purified" appears without referencing to Footnote 38. This has now been corrected by inserting reference to Footnote 38 where necessary, and inserting the phrase "subgenomic segments that have not been purified to the extent required in Footnote 38" at other places.

A correspondent discussed "EK1CV," defined in Footnote 40 as the "the use of an EK1 host and a vector certified for use in an EK2 system." He points out that certain EK1CV systems provided containment comparable or almost comparable to EK2, while others are only slightly better than EK1. This is true. However, in all cases the level of containment is higher than EK1. The cases in the Guidelines where EK1CV containment is specified as an option were so recommended by the RAC on the basis of the recommendation of the April 6-7, 1978, Virus Working Group (Appendix F to July 28, 1978, Environmental Impact Assessment).

**Section III-A-3. Lowering of Containment for Characterized or Purified DNA Preparations and Clones**

As in many other sections of the Guidelines, commentators have ex-

pressed their opinions in both general and specific terms. A commentator states that there is no information at present to "show any hazard deriving from recombinant DNA or organisms harboring such DNA \* \* \*". In particular, it would seem quite clear that characterized cloned eukaryotic DNA elements in *E. coli* pose no conceivable hazard." Pursuing this line of reasoning, the commentator argues for elimination of regulation and, in particular, suggests that "consideration be given to a change in the Guidelines so that institutional biohazard committees could be empowered to exempt characterization clones from further regulation."

The proposed revisions in the Guidelines empower the IBCs to give approval for a single-step reduction in physical or biological containment upon receipt of evidence of characterized of a clone and its freedom from harmful genes. Further reductions, or cases involving primate DNA or lowering of containment levels below PI + EK1, require prior approval by NIH. I do not believe it prudent to accept the commentator's recommendation at this time.

Two comments were received on the criteria for the terms "purity" and "free from harmful genes." Once commentator expressed concern over the inadequate definition of these terms. He believes they are not defined with sufficient precision to guarantee uniform decisions, particularly when the authority to lower containment by one step is left with the IBC. The commentator suggests more rigorous criteria for purity (other than 99 percent) and a broader definition of "harmful gene" to include the concept "that genes which might not be harmful when expressed in their original organism could indeed be harmful if expressed out of context in an unrelated organism."

The other correspondent discussed Footnote 41 which requires that the "desired DNA represents at least 99 percent (w/w) of the total DNA in the preparation" before it may be considered "purified." He stated: "Its adoption reflected the supercautious mood prevalent at that time rather than a clear-cut scientific judgement. In my view, requiring that a DNA fragment should be 90-95% pure (as judged by at least two different analytical procedures) to remove it from the shotgun classification is more realistic and no less safe. Requiring that a DNA fragment be >99 % pure prior to cloning asks for the most stringent and detailed documentation without any real advantage."

The term "purity" is very explicitly defined in Footnote 41. The requirement is that the desired DNA must represent at least 99 percent (w/w) of



the total DNA in the preparation. In addition, at least two biochemical or physical procedures are required for verification of purity.

Footnote 3 gives guidance to the IBCs on many factors to be considered before deciding that DNA recombinants are "free of harmful genes." Further specificity seems unwarranted. I believe that to broaden the definition to include the concept of "harmful" when a gene is expressed out of the normal physiological context would be contrary to the intent of Footnote 3. In considering this issue, I have noted that in the proposed revised Guidelines, different terms are used: i.e., in Section III-A-3, "and the absence of harmful genes established"; in Section III-A-3-a, "are free of harmful genes"; in section III-A-3-b, "and there is sufficient evidence that it is free of harmful genes." These have all been changed (also in Footnote 3 and Section I-D-6) to "and the absence of harmful sequences established." I have also decided that the 99 percent criterion should be retained in the present revision of the guidelines; but this point will be reconsidered by the RAC as a possible item for future revision.

#### Section III-B. Experiments with Other Prokaryotic Host-Vectors

Several correspondents addressed the use of hosts other than *E. coli* K-12. They pointed out that many experiments with such hosts are "inadvertently prohibited," and suggested wording to allow experiments in hosts other than *E. coli* K-12 which do not meet the criteria for HV1.

In the proposed revised Guidelines, experiments with prokaryotic hosts other than *E. coli* K-12 fall into the following classes: (i) Self-cloning, exempted under the exemption I-E-3; (ii) return of DNA segments to non-HV1 host of origin, Section III-B-2; and (iii) use of HV1 systems, Section III-B-1. I agree that there are many safe experiments which fall into none of the above three classes but which should be allowed under specified containment levels. The proposed revised Guidelines, at the beginning of Section III, stated, "... (or the assignment of levels to experiments not explicitly considered here) may be expressly approved by the Director, NID, on the recommendation of the Recombinant DNA Advisory Committee (RAC)." This language has been retained in a slightly modified form in the final Guidelines. In addition, similar language is now repeated in a new Section III-B-3 and at the end of Section III-C-5.

A specific example of this type of problem was provided by a commentator who cited experiments he would like to perform involving recombinant DNA from *Bacillus popilliae*, a patho-

gen for the Japanese beetle, and *Bacillus thuringiensis*, a pathogen of pest caterpillar larvae. He asked for clarification of what containment levels would apply under the proposed revised Guidelines.

The experiment could be considered under several different provisions. If data are submitted on natural exchange of DNA between *B. popilliae* and *B. thuringiensis*, these organisms could be listed in a future version of Appendix A as falling under exemption I-E-4. Or under the new paragraph III-B-3 which has been added to the Guidelines, containment levels could be set for these experiments.

#### Section III-C. Experiments with Eukaryotic Host-Vectors

A general issue raised by one respondent concerns the stipulation that some experiments will be assigned containment levels on a case-by-case basis. The commentator is concerned that this approach ignores the need for minimum standards which can serve as a guide for research workers.

I believe that the case-by-case analysis prescribed for many experiments involving the employment of viral DNA as a vector reflects the caution exercised over the use of such DNA. Each such experiment is thus prohibited until the RAC has had a chance to weigh the scientific evidence and propose whether the experiment should proceed and, if so, to assign appropriate physical and biological containment levels.

I have accepted several other recommendations for changes in this section. Two commentators offered new language for the section dealing with requirements for the employment of defective adenoviruses as cloning vectors. They noted that new mutants of Ad5 or 2 in which the entire transforming region has been deleted have recently been isolated. These mutants can only be propagated in adenovirus-transformed cells. The commentators suggested that the language in Section III-C-1-c-(1)-(a) be generalized to state: "Human adenoviruses 2 and 5, rendered unconditionally defective by deletion of at least two essential genes, with appropriate helper, can be used under P3 conditions to propagate DNA sequences from \* \* \*." I believe this is justified, and the Section has been modified by changing the word "capsid" to "essential."

A correspondent stated that Section III-C erroneously equates nonproductive infections with nonpermissive cells. He pointed out that in certain situations nonproductive infections may result from infection of permissive cells. I agree. Accordingly, the phrase "to transform nonpermissive cells in culture" has been eliminated at a number of places in Section III-C,

and more appropriate language has been substituted.

The same correspondent pointed out that in Section III-C the word "intact" is not appropriate because as soon as a foreign sequence is introduced, the viral DNA is no longer intact. I agree. The wording in the relevant sections has been changed from "intact" to "whole."

#### Section III-C-2. Invertebrate Host-Vector Systems in Which Insect Viruses Are Used to Propagate Other DNA Segments. Section III-C-3. Plant Viral Host-Vector Systems. Section III-C-4. Plant Host-Vector Systems Other than Viruses

I have considered the comments for these three sections in a single group.

A witness questions "the necessity for EPA registration of an entomopathogenic organism in lieu of simply meeting the criteria of EPA for a temporary exemption from a requirement of tolerance in the environment."

In the proposed revised Guidelines published in the FEDERAL REGISTER on September 27, 1977, "baculoviruses which have been registered by the Environmental Protection Agency" are specifically discussed in the section dealing with invertebrate host-vector systems in which insect viruses are used to propagate other DNA segments. The writer is apparently addressing this section and requesting that the EPA registration not be required but merely "the criteria of EPA for a temporary exemption from a requirement of tolerance in the environment." The analogous section (III-C-2) in the proposed revised Guidelines published in the FEDERAL REGISTER on July 28, 1978, does not in fact refer to EPA registration as a specific criterion. It indicates that experiments in which insect viruses are used to propagate other DNA segments will be evaluated on a case-by-case basis by the Recombinant Advisory Committee. Information required for a judgment includes host range restrictions, and infectivity, persistence, and integration of the viral DNA. Data submitted by the requesting investigator on whether EPA has registered a given insect virus or whether it meets the EPA criteria for a temporary exemption from a requirement of tolerance in the environment will be considered by the RAC.

The same witness also questioned the validity of the statement in Section III-C-3 that "the plants should be grown under P1 conditions—that is, in either a limited access greenhouse or plant growth cabinet which is insect-proof" and suggested substitution of the term "insect-restrictive" rather than "insect-proof," since the latter term implies higher containment. I



concur with the recommendation and have made the change.

On the other hand, I do not agree with the opinion of the correspondent who questioned the relevance of P1 or P2 containment conditions to experiments in which recombinant DNA is cloned in higher plants. The correspondent believes that higher plants containing nonviral recombinant DNA should not require any containment. The proposed revised Guidelines (pages 33082 and 33084 in the *FEDERAL REGISTER* July 28, 1978) specifically define special P1 and P2 conditions for work with plants. I do not believe that recombinant DNA work with higher plants should now be done with no containment at all.

Finally, I have considered the request of two correspondents discussing employment of the tumor insertion plasmid (Ti) of *Agrobacterium tumefaciens* as a cloning vector. They suggest adding the following sentence to Section III-C-4: "Inoculation of hosts with HV1 approved *Agrobacterium* containing the DNA recombinants requires P2 physical containment." I do not believe inclusion of the sentence is warranted at this time. Data on the system can be submitted to the RAC for approval as an HV1 system. If approval is granted, the RAC at that time can recommend the appropriate containment level.

#### Section III-D. Complementary DNAs

Two correspondents were concerned over the possibility of eukaryotic DNA being expressed in prokaryotic cells. They noted that genes cloned via a shotgun experiment will probably not be expressed because they retain their intervening sequences and the resulting RNA is not likely to be processed. On the other hand, complementary DNA prepared from messenger RNA could serve in turn as a template for synthesis of the same RNA within the prokaryotic cell. They suggest that a "distinction should be made between eukaryote DNA and cDNA formed from mRNA."

In responding, I must note that containment levels for eukaryotic DNA were developed on the assumption that such DNA, no matter what the source, could be expressed. The proposed Guidelines set the same containment levels for eukaryotic DNA and cDNA formed from functional eukaryotic mRNA. For cloning of viral DNA into *E. coli* K-12, however, there are differences in the containment levels depending on whether one is using the viral DNA itself or cDNA from viral mRNA (see Table III). The probable future uses of cDNA copies of functional mRNAs are discussed in the Introduction and Overview of the Director's Decision (*FEDERAL REGISTER*, July 28, 1978, pp. 33044 and 33047).

#### Section III-E. Synthetic DNA

A correspondent argued that the discussion of appropriate containment levels for synthetic DNA that codes for harmless polypeptide products "makes no sense." He asks, "Why is any containment required for a harmless product?" and recommends the following alternative language for this section: "If the synthetic DNA sequence codes for a harmless product or if the synthetic DNA is not expressed *in vivo*, the organisms containing the recombinant DNA are exempt (4) from the Guidelines."

In reply, the term "harmless product" refers to the normal toxicity or pathogenicity of the protein and not necessarily to the remote possibility of its otherwise disrupting the physiological balance of the organism in which it might inadvertently be introduced. I believe that the language of the NIH-proposed revision should remain as published, since the three paragraphs describing containment for synthetic DNA clearly describe three distinct concepts. The provisions of Section III-E are consistent with those of III-A-3 dealing with containment levels for purified or characterized DNA.

#### IV. ROLES AND RESPONSIBILITIES

##### RESPONSIBILITIES OF THE INSTITUTION (GENERAL)

##### Institution

The general responsibilities of the institution are to ensure appropriate review and implementation procedures for all of the institution's recombinant DNA activity that is covered by the Guidelines. Below are a number of general institutional responsibilities that were addressed in correspondence and by witnesses at the DHEW public hearing.

**Exercising Institutional Authority.** Both groups of commentators stated that the Guidelines should permit the institution to set new requirements beyond those of NIH. In the Guidelines, the institution has this authority, and a provision has been added specifically stating that the institution may establish requirements and procedures for the general implementation of the Guidelines, including additional precautionary steps if deemed appropriate. It should be noted, however, that these Guidelines and the standards they embody are conservative and in no way constitute a minimum set of requirements.

**Establishing an Institutional Biosafety Committee.** Requirements for membership on the Institutional Biosafety Committee (IBC) drew substantial attention in the letters and at the public hearing. Much of the comment was directed to mandating various representation. Some commentators sug-

gested that a local public health official and a nondoctoral person from a laboratory technical staff serve on the committee. Others recommended mandating community leaders who are "in touch with grass roots attitudes," including "environmentalists." Others suggested that the membership reflect the demographic distribution of the community in which the institution is located. Requirements for membership distribution by age, sex, income level, professional background, and other variables were mentioned. It was suggested that at least two members be custodial or janitorial workers. Others recommended that there be at a minimum one physician trained in infectious diseases, one epidemiologist, and one environmental scientist.

Other commentators and witnesses suggested various ratios of scientists and nonscientists serving on the committee. Some urged that one third of the membership represent "the interest of the community" and another third "scientific disciplines related to risk assessment." It was also suggested that nominating procedures be specified for selecting community representatives.

On the other hand, some commentators believed that the proposed revision was presumptuous in mandating lay representation on this committee, especially when the university may already have several lay committees for oversight.

Others suggested that the minimum membership for an IBC be raised from five to seven. The minimum of five members is recommended to take into account small universities with few projects. In these and many other cases, five is sufficient, and it remains as the minimum. Membership recommendations in the revised Guidelines attempt to balance professional expertise with members who represent the interest of the surrounding community. As pointed out by one correspondent, however, the IBC, in contrast to human-subject committees where broad concepts of social and ethical values are considered, is in large part an expert committee whose essential function is to evaluate research protocols in respect to containment levels, using the explicit instructions of the Guidelines. Rigid quotas are not necessary. Indeed, many small academic institutions would have considerable difficulty meeting specified demographic requirements. The IBC criteria are flexible to permit the institution to select a committee capable of fulfilling its responsibilities.

The DHEW Committee carefully reviewed all the comments and considered at great length membership requirements for the IBCs. On balance, it was decided that the interest of the surrounding community could be



served, as one commentator suggested, by "at least two members." In addition, at least 20 percent of the committee shall not be affiliated with the institution and shall represent the interest of the surrounding community with respect to protection of the public health and the environment. Moreover, nomination procedures need not be specified, but should be left to the discretion of the institution for the selection of these members.

With respect to conflict of interest, some commentators recommended that IBC members be prohibited from any direct involvement in recombinant DNA or closely related research unless the member is a laboratory worker. The conflict-of-interest provisions in the Guidelines respond to these concerns while reflecting the paramount need for relevant scientific competence on the IBCs.

A commentator stated that "peer review does not adequately protect the public," citing instances of noncompliance with the Guidelines at two NIH grantee institutions. It should be noted that the two cases in point involved administrative violations and presented no risk to the public health or the environment.

Some of the commentators from the private sector expressed concern that the financial conflict-of-interest statement required in the Guidelines might be interpreted as denying IBC membership to any member of a company. Others felt that a requirement for public members would present problems of protecting confidential information. However, at a meeting of the DHEW Committee and representatives from the Pharmaceutical Manufacturers Association, it was agreed that public members could and do serve on the committees. Some are asked to sign agreements to honor confidentiality of proprietary and patent information.

**Health Surveillance.** This area was one of deep concern to some witnesses and correspondents. Witnesses at the September 15 hearing made several suggestions concerning medical surveillance, and correspondents suggested that the term "medical surveillance" be changed to "health-risk surveillance" or "health surveillance." That suggestion has been adopted in the Guidelines.

Several commentators and witnesses urged that health surveillance programs be required in the Guidelines. Concern was expressed that without such a requirement different standards and different programs would result. In addition, there were many suggestions from commentators, including the Occupational Safety and Health Administration (OSHA), about what should constitute a health surveillance program—for example, com-

plete medical histories, periodic medical checkups, and serial serum samples. It was recommended that laboratories be required to keep official OSHA health and safety log forms, and that records be kept of all agents use, all modified organisms created, and all laboratory-acquired illnesses.

Several commentators also called for a clearinghouse, to be established at the Federal level, at which copies of all health surveillance plans and records would be filed. It was urged that NIH maintain such data, including records of workers in laboratories using recombinant DNA techniques, with particular regard to instances of possible work-related illness. There were also several suggestions for a national epidemiologic monitoring and surveillance program to be supported by DHEW. Such programs might, as one commentator suggested, promote national standards for health surveillance specific for each class of organisms and group of experiments. And finally, there were suggestions for ongoing epidemiologic and biostatistical analysis of data as they are accumulated to permit early detection of trends.

I reviewed these issues in the Decision document accompanying the proposed revised Guidelines as published in the *FEDERAL REGISTER* July 28, 1978. As I noted in that document, the issue of medical monitoring is one of considerable interest to NIH and is not unique to recombinant DNA research. The "state-of-the-art," however, is primitive in terms of effective monitoring of workers' health generally, and particularly in recombinant DNA research, where there is no known hazard.

One commentator noted that the Cambridge, Massachusetts, city ordinance for recombinant DNA research requires the institution, as part of its health surveillance responsibility, to monitor survival and escape of recombinant DNA organisms in each laboratory worker engaged in this type of research, as by the testing of intestinal flora. Intestinal flora sampling is being undertaken at MIT. NIH will follow the MIT program closely. This is not the time, however, to propose extension of that experiment to general practice.

We recognize the need to aid the institutions as much as possible in this important area. The laboratory Safety Monograph provides extensive detail and guidance. It suggests monitoring illnesses, collecting serum samples, and keeping a register of agents handled. Moreover, the Guidelines now require the institution (rather than the principal investigator) to determine, in connection with each project, the necessity for health surveillance of relevant personnel and to conduct a health surveillance program appropri-

ate to the project. And the Memorandum of Understanding and Agreement will include reference to health-surveillance programs associated with the project.

In response to the calls for a national clearinghouse, it should be pointed out that the NIH Office of Recombinant DNA Activities (ORDA) has been designated in the Guidelines to receive, review, and maintain certain medical and accident information. Through ORDA, NIH will have a collection of essential data which should provide the ability to discern if certain experiments result in unique health problems. It is emphasized, however, that for any health surveillance to be truly effective, it must be conducted at the local level.

#### RESPONSIBILITIES OF THE INSTITUTION (SPECIAL)

The special responsibilities of the institution include establishing general policies, appointing the Institutional Biosafety Committee (IBC), appointing a Biological Safety Officer (BSO) where required, and reviewing and implementing procedures applicable to the submission of the Memorandum of Understanding and Agreement (MUA). A number of commentators and witnesses addressed these requirements.

One commentator recommended that the signature of an institutional official not be required on the MUA (in Appendix C of the July 28 revision), but that the IBC chairperson should represent the institution. The signature of an institutional official on the MUA is requisite, for that individual is authorized to act for the institution and assume on its behalf the obligations imposed by the Guidelines. If the institution so wishes, however, it may designate the IBC chairperson as the responsible official for MUAs that do not require prior NIH approval. This is newly noted in the Guidelines and the Administrative Practices Supplement (APS), which now incorporates Appendix C.

The correspondent also recommended that MUAs for fellowships, as found in Appendix C, be deleted as an unnecessary duplication of effort. This recommendation is sound, for it is duplicative to require an MUA when the projects are registered. Thus, MUAs will not be required with fellowship applications.

Another correspondent called for clarification of the difference, if any, between the IBC's procedures for review of NIH-funded and non-NIH-funded projects. The information required for NIH- and non-NIH-funded projects in an institution receiving NIH support for recombinant DNA research is similar. Further information on the requirements has been included in the APS. For purposes of IBC



review and monitoring responsibilities, there should be no distinction between NIH- and non-NIH-funded projects.

Another commentator urged that the Guidelines give greater detail on the types of protocol changes for which a new or revised MUA must be sent to NIH. Information previously contained in Appendix C has now been added to the Guidelines to clarify this point, and further information is contained in the APS.

Another commentator suggested that the institution be required to notify a local Health Systems Agency upon filing an application for Federal support of recombinant DNA research. This is not applicable to HSA responsibilities under section 1513(e) of the PHS Act and therefore is not mandated.

Another correspondent requested that Appendix C be mandated. The test of Appendix C, now in a supplement to the Guidelines (the APS), has been extensively rewritten, and many of its features have been incorporated in the Guidelines for purposes of clarification. I agree that the provisions now in the Guidelines should be mandatory.

**Institutional Compliance.** A commentator challenged the right of NIH to require an institution to hold that all principal investigators, irrespective of source of funding, must follow the Guidelines. This requirement, however, is vital to the maintenance of uniform standards and is therefore retained. On the other hand, research supported by another Federal Agency need not be registered with NIH when that agency maintains a registry and provides NIH with essential information.

Another commentator suggested delegating responsibilities for all enforcement of the Guidelines to the institution (IBC), with ORDA receiving periodic reports from the committees on the research they are regulating. There are several reasons such a course would be unwise at this time. Exercise of any discretion is a new responsibility for the IBC's. Uniformity and expertise must be demonstrated by verification through NIH review. A great deal of standard-setting, necessarily central at present, is yet to be done through case-by-case analysis.

One commentator requested that the NIH notify both the IBC chairperson and the institution when it was reviewed each action of the IBC according to the information submitted on the MUA. This, I believe, would strengthen coordination of compliance efforts. The final Guidelines accordingly require the double notification.

It was also suggested that NIH provides a statement that it has certified the institution and finds it to be in compliance. This request is related to

requirements in State regulations that go beyond the Guidelines. However, NIH plans to provide official documentation to institutions in States requiring such information. The subject will be further treated in the APS.

Another commentator urged NIH to devise a system to protect those who report possible violations. This issue was reviewed in my Decision accompanying the proposed revised Guidelines (FEDERAL REGISTER, July 28, 1978, p. 33065), where I noted that grievance procedures for workers under the Guidelines were not considered necessary because OSHA rules and regulations already provide such a mechanism. However, witnesses at the September 15 hearing and comments from OSHA state that the Occupational Safety and Health Act does not cover employees of State and local governments unless the State operates under an OSHA-approved State plan covering health and safety practices and grievance procedures. Only 23 States currently have such plans. But other States presumably have similar statutory protection, and it would be presumptuous of NIH to attempt to detail specific grievance procedures in all jurisdictions. The Guidelines require the reporting of violations and allow the reports to be made to NIH by anyone. The institutions, I believe, will accept such reports in a positive light and as an important aid in maintaining compliance with the NIH standards.

#### *Institutional Biosafety Committee (IBC)*

The principal functions of the IBC are to review and oversee all recombinant DNA projects with respect to compliance with these Guidelines and to advise the institution and ORDA whether the proposals and the research so comply. A number of issues concerning IBCs were addressed by the commentators and witnesses at the September 15 hearing, including delegation of authority to the IBCs, public representation on the committee, and public access to its proceedings.

**Delegation of Authority.** Several correspondents and a number of witnesses at the September 15 public hearing took exception to the delegation of authority to the institutions and their IBCs to act on certain experiments without prior NIH approval. One witness noted that there has been a 4 to 15 percent error rate by the IBCs. He also noted that NIH review did not entail inordinate delays, citing the usual review at ORDA as taking only 4 to 5 days. He urged that NIH retain the present two-level system of review requiring prior NIH approval for all projects. The data here do not take into account additional referrals of MUSs between

ORDA and various NIH Institutes supporting such research. These have introduced delays of may days or weeks in processing. Other commentators recommended quite the opposite—that greater latitude be given the IBCs to assign containment levels for experiments.

The reason for the delegation of authority is extensively discussed in my Decision and the Environmental Impact Assessment accompanying the July 28 publication of the proposed revised Guidelines. As stated in the Decision document, the increased responsibility of the institution is in response to comments calling for a simpler administrative process and more local responsibility. It is also a recognition of the practical requirements for enforcement of standards for use of such highly varied and complex technology in many institutions spread over a vast area. As stated by the House Committee on Interstate and Foreign Commerce in its report of March 28, 1978, on the Recombinant DNA Act: "... the appropriate portions of the administrative requirements of section IV of the NIH Guidelines are a reasonable model upon which the Secretary could base administrative regulations. In particular the current practice in the NIH Guidelines of delegating to local biohazard committees most of the responsibility for the inspection of the facilities and the approval of the specific safety requirements appropriate to each project or activity is an effective and relatively inexpensive administrative mechanism." Thus, the delegation of increased responsibility at the local level is not primarily to facilitate an increased volume of research, as suggested by a commentator, but rather to place this function at the most appropriate location for initial enforcement of the Guidelines. It should be noted, however, that MUAs, before going to ORDA, go to the NIH Institute funding the research, and there have been delays of days or weeks at this level, adding substantially to the time required for processing. We will consider means to simplify procedures so the ORDA can respond in a timely fashion to the institutions.

The DHEW Committee carefully considered the issue of prior NIH approval. On the basis of that review, the Guidelines now specify the circumstances in which prior approval is required, with greater detail provided in the APS. In addition to the five categories of experiments requiring prior approval in the NIH proposal, prior approval is now required, on the recommendation of the DHEW Committee, for the first project to be conducted by an institution and the first project in a facility at P3 containment.



It should be emphasized that while the delegation to the IBCs permits initiation of all other research at the local level, the NIH review and approval of all research under the Guidelines will continue as before. All protocols not found to be in conformance must be modified. Given the slowly increasing sophistication of investigators and IBCs alike, plus the provision in the Guidelines of explicit standards for performance of their duties, I am confident that this delegation will in no sense present risks to the health or the environment.

It should also be noted that some commentators still regard proposed administrative procedures as "excessive and disproportionate when measured against the perceived risks." They are especially concerned that the work of the IBCs is taxing the human and financial resources of the institution. That a burden is placed on the local institutions cannot be denied, but the responsibility is better delegated than retained at the Federal level. As we learn more, there will presumably be less and less need for formality and centralized review in the governance of this research. In anticipation of probable decentralization with time, creation of the local capability must begin without delay.

Another commentator urged that the Guidelines be extended to all hazardous biological research. As stated in my Decision of July 28, I do not believe we can or should extend the Guidelines to other research at this time. However, the entire area of laboratory safety is of prime concern to NIH and the subject of constant review and attention. NIH activities in this area are described in the Environmental Impact Assessment published with the Guidelines as proposed in July. It should be noted that some IBCs, as one correspondent pointed out, assume the added duty of monitoring work with known pathogens that is not related to recombinant DNA technology.

In view of the delegation, some commentators urged that there be more financial support for the operations of the IBC. It was recommended that NIH require some percentage of the overhead charged on recombinant DNA research proposals to be earmarked for operation of the IBCs.

Concern has been expressed in the past about the cost of the IBC operations. As stated before, NIH already pays for the operations of such committees through reimbursement of so-called indirect costs of research. I do not believe there is need at this time to separate them from other indirect costs of the institutions.

**Reduction of Containment Levels.** A number of commentators and witnesses questioned the authority of the

IBCs to lower containment requirements for certain experiments. On the other hand, many believe the IBCs should be authorized both to reduce and to raise containment levels. It should be understood clearly that the IBCs' authority to lower containment levels is quite limited and governed by strict standards and procedures set forth in the Guidelines. NIH is notified of all such discretionary actions. It will review them and require that any failures to come up to the standards of the Guidelines will be corrected.

Specifically, the IBC can reduce containment levels only for experiments using purified DNA and for characterized clones. Standards and procedures for the former action are stated in Section III-A-3-a of the Guidelines and in Footnote 41; those for the latter action, in Section III-A-3-b and in Footnote 3. Standards for both actions appear also in the IBC section of part IV of the Guidelines and in greater detail in the Administrative Practices Supplement. Further, it should be noted that NIH approval is required for any lowering of containment levels below PI + EK1, or by more than one step, or for experiments involving primate DNA.

Specific authority is granted to the institution (Section IV-D-1) to establish requirements deemed necessary for the implementation of these Guidelines. The IBC, then, can raise containment levels. The national standards, however, are very conservative, and in my view, to raise them generally or for characterized clones and purified DNA is unwarranted.

**Appeals.** Several commentators advocated, in light of the authority delegated to the IBCs, procedures for "appealing a decision of the local IBC against a project or against a certification of facility." The Guidelines do not prescribe an appellate mechanism. A full partnership of investigators and their institutions is intended in maintaining compliance with the Guidelines. The investigators and the IBCs must not be cast in adversary roles, and NIH will make every effort to promote their cooperation. We will be available on request to provide technical advice and consultation with principal investigators and institutional committees alike.

**Emergency Plans.** The IBC has responsibility to review and approve emergency plans. A number of commentators suggested greater detail in the Guidelines on the emergency procedures to be employed, including specification for cleanup procedures to be followed should there be a spill or accidental release of organisms into the environment. Other commentators suggested that the Guidelines set national standards for the handling of

emergency spills. Several urged that the biosafety officer at each institution be charged with responsibility for drafting such plans.

The Laboratory Safety Monograph presents guidance on pages 194-196 on procedures to be followed in emergencies. Some of that information is now included in the Guidelines to emphasize its importance. The monograph will be revised further, in response to comments, to provide greater detail and to include emergency numbers at NIH and the Center for Disease Control that can be called on a 24-hour basis. The two agencies will provide consultation and direct assistance if needed. In addition, the Guidelines specify that the institution shall cooperate with the State and local public health departments and report to them any illness or laboratory accident that appears to be a hazard to the public health. And the IBC chairperson is responsible for notifying the institution and NIH, within 30 days, of problems with the Guidelines, violations, or significant research-related accidents or illnesses, unless the chairperson finds that the PI has done so.

**Public Access.** Several witnesses at the September 15 hearing and many commentators urged greater public access to proceedings of the IBC. The proposed revised Guidelines required that minutes of the IBC meetings be made available to the public upon request. However, there were several suggestions for further requirements. Witnesses urged that the IBC meetings be publicized and open to the public, except for those specifically dealing with proprietary or other confidential information. Suggestions were made to enhance public participation through evening meetings of the committee and the use of lay summaries of research proposals. Procedures were recommended for announcing IBC meetings. Others recommended that all MUAs and reports of inspections be made publicly available.

The DHEW Committee spent a great deal of time reviewing comments about this portion of the Guidelines. In my Decision accompanying the proposed revision of July 28, I noted that possible discussion of proprietary and patentable information often precludes open IBC meetings. I did urge, however, that local committees have open meetings when possible and that they be publicly announced.

In response to the issues raised, and in view of the increased responsibility given to the local institutions, the final Guidelines require, in addition to public representation on the committee, public access to proceedings of the IBC. Institutes are encouraged to open IBC meetings to the public whenever possible, consistent with the protec-



tion or privacy and proprietary interests.

In addition, the IBC is to forward to NIH any public comments made on its actions and the committee's response to them. And all IBC documents that NIH must make available to the public, such as the funded research proposals, are also to be made available, upon request, at the local level. These include reports of serious accidents and of problems with and violations of the Guidelines; also all NIH reports to institutions when MUAs (including modifications of ongoing projects) are not in compliance. Likewise, minutes of the IBC meetings and inspection reports will be made available. The intention of the Guidelines in all these changes is to enhance public accountability at the local level.

#### *Biological Safety Officer*

There were a number of comments concerning the roles and responsibilities of the Biological Safety Officer (BSO). Several witnesses at the September 15 hearing recommended that whenever recombinant DNA research is being conducted at an institution, such an officer be appointed and required to serve on the IBC. It was also recommended that the BSO have a full-time position. The Committee considered the role of the BSO at some length.

The Guidelines do specify that all institutions conducting work at the P3 and P4 levels must have a BSO. The officer is required at those levels because the sophisticated equipment and facilities require special abilities. The Laboratory Safety Monograph (p. 191-193) outlines the qualifications and role. But the Guidelines do not mandate such an officer for P1 and P2 work because the potential risk at those levels is minimal and the expertise readily available for laboratory safety. The Committee concurred with this view.

Other commentators recommended that the Guidelines assign to the BSO responsibility for monitoring, keeping records, and health surveillance. The DHEW Committee reviewed the qualifications of BSOs, noting the absence of certification procedures for such a new and ill-defined discipline. Accordingly, it was agreed that certification requirements should not now be stipulated for BSOs and that flexibility should be encouraged to permit a BSO to have responsibilities for such activities as health surveillance. As noted in the LSM, one can call on the environmental health and safety program at the institution to assist in a variety of the duties suggested for the safety officer.

The BSO is responsible for developing emergency plans, and the NIH will provide assistance for program devel-

opment. But in my view, it is far more sensible at present to begin emergency plans at a local level than to attempt to develop them on a grander scale until any hazards are better understood. Unless the principal investigator has already done so, the BSO is also responsible for providing reports to the IBC and the institution on problems with and violations of the Guidelines and on all significant research-related accidents and illnesses.

#### *Principal Investigator*

As stated in the introduction to part IV, safety involving recombinant DNA molecules depends in the first instance on the individuals conducting the research. The Guidelines are designed to help the Principal Investigator determine the safeguards that should be implemented, and it is his or her responsibility to ensure that the purpose of the Guidelines is fulfilled. A number of the comments were devoted to the PI's role in laboratory safety and training.

*Training.* Many of the correspondents and several of the witnesses at the September 15 hearing recommended training programs for all laboratory personnel, including custodial personnel, the members of the Institutional Biosafety Committee, the Biological Safety Officer, and all relevant institutional officials. One commentator recommended that laboratory workers in P2 or higher facilities take and pass training courses or demonstrate equivalent competency before working directly with organisms containing recombinant DNA. Further, a centralized and uniform certification process for workers at the P3 or P4 level was advocated. It was urged that the Guidelines not be revised until there are uniform procedures for training certification of all biosafety officers and all recombinant DNA laboratories at the P2 or higher levels. Some suggested the Biological Safety Officer should be responsible for the certification process.

A number of commentators advised further that the Guidelines specify components of training for a program available to all potentially exposed workers. It was also recommended that the PI make available copies of approved protocols that describe potential biohazards and precautions, not only to the research personnel but also to the custodial staff. It was further suggested that NIH and OSHA should jointly sponsor technical and educational programs for IBC members and Biological Safety Officers.

I appreciate the concern regarding the quality and uniformity of training. As I stated in my Decision document (July 1978), NIH is responding to this by placing a high priority on the development of training standards and

courses. For example, we are supporting, as noted previously, a working panel of the American Society for Microbiology that is considering standards for training in microbiological techniques for recombinant DNA research. When a report is submitted to NIH, it will be shared with institutions, IBCs, PIs, and BSOs. National certification of proficiency in any research technology is fraught with problems, especially in areas in which knowledge is increasing rapidly.

NIH is already sponsoring and developing courses on these standards of training. For example the University of Minnesota School of Public Health has developed and conducted a series of short courses on "Biohazard Containment and Control for Recombinant DNA Molecules" under the sponsorship of the National Cancer Institute's Office of Research Safety. The objective is to instruct laboratory workers on the principles of safety in the research laboratory and, particularly, on their application to the safe handling of recombinant DNA molecules. To date, six courses have been presented. A total of 221 participants from 97 institutions have attended. They have come from 7 government laboratories, 34 private or industrial laboratories, and 56 universities.

The Office of Research Safety, NCI, is also developing a training course for biosafety officers on practices and procedures for the control of biohazards in the research laboratory. The purpose is to equip biosafety officers with the basic knowledge and skills to carry out effectively the responsibilities specified in the NIH Guidelines. Detailed instruction on methods for evaluating, certifying, and monitoring physical-containment safeguards will be offered. Guidance will also be provided on how to organize, plan, develop, and conduct a comprehensive biosafety program.

NIH plans to further the biosafety training efforts of institutions by providing on-site consultation. The program will be designed to assist institutions and their IBCs, biosafety officers, and laboratory workers in effectively carrying out the requirements of the Guidelines. Biosafety professionals will be available to visit institutions and assist them in evaluating and improving their safety programs. These professionals will also be available to help solve specific problems in physical containment. A principal element of the program will be to promote good laboratory practice and to reinforce its importance.

Training of laboratory workers is a continuous process required under the Guidelines. One commentator expressed uncertainty as to who has the responsibility for seeing that personnel are trained in safety practices and



techniques. The DHEW Committee reviewed this matter, and on the basis of the review, the responsibilities have been clarified. The institution is responsible for ensuring appropriate training for IBC chairpersons and members, laboratory staff, and the BSO. The IBC chairperson will brief the IBC members and provide whatever information on training is required for them to fulfill their responsibilities. To the PI is delegated responsibility for training all the laboratory workers involved in the project.

**Safety Practices.** The PI is responsible for correcting work errors and conditions that may result in the release of recombinant DNA materials. Several commentators suggested that any accidental release of recombinant organisms, regardless of suspected pathogenicity, be reported to the proper health authorities. The Guidelines now require the institution to report to State and local health departments any significant research-related illness or accident that appears to be a hazard to the public health.

Another commentator suggested that the PI be required to halt ongoing research if any problems result in a failure to meet assigned containment requirements. It was suggested that the research be halted for 24 hours while a report is made to the IBC. The IBC would then certify in writing that the necessary repairs have been made. The Guidelines require reporting and correction of such problems by the investigator, but they do not specify a time limit except that reports must be made to NIH within 30 days on any significant problems with the Guidelines, on violations, and on all significant research-related accidents and illnesses. Nor do they require the IBC to document the repairs. While these mandates are not necessary, the institution should consider setting such policies as deemed necessary. The Laboratory Safety Monograph and the Guidelines contain increased information on health surveillance to assist the PI in his responsibilities in this area.

**Exemptions and Exceptions.** Another commentator suggests that the PI receive IBC approval before petitioning the NIH for exemptions to the Guidelines or exceptions to the prohibitions. In light of the enhanced responsibilities of the local IBCs, it is appropriate for them to review proposals for exceptions to the prohibitions. Accordingly, the Guidelines now state that proposals to NIH must be submitted with the concurrence of the IBC.

Proposals for exemptions from the Guidelines deal with alterations in standards applied to all engaged in this research. Scientists may send those proposals directly to NIH for the considerations of the RAC with

notice to the IBC. Note of exemptions granted will be sent to all IBCs. Experiments that are exceptions to the prohibitions require approval at the national level, after which they must be reviewed and approved by the IBC. An MUA must then be approved by NIH before the experiment may be initiated.

**MUAs.** Several commenters suggested that the Guidelines be clarified with respect to the types of experiments that may not be started prior to NIH approval. As noted previously, the Administrative Practices Supplement is responsive to the suggestion, and more guidance is given in the section of the Guidelines on "Institutions" (IV-D-1) to clarify the preparation and submission of MUAs for new and modified experiments.

**Publication.** The Guidelines recommend that published research articles specify the containment procedures used. A commentator advocates that this be required. The issue has been raised before, and it remains our view that NIH neither can nor should control what must be included in scientific publications.

#### RESPONSIBILITIES OF NIH (GENERAL)

##### *Due Process Considerations*

A number of commentators spoke on the issue of public participation, including how best to inform the public and ensure public access to NIH proceedings. A number of commentators and witnesses at the September 15 hearing focused on the provisions calling for "appropriate notice and opportunity for public comment." Several suggested that those provisions be described in greater detail in the Guidelines. Other commentators urged that labor and environmental representatives, consumer advocacy groups, public health officials, and government agencies with potential regulatory responsibility have full access to decision-making.

Some commentators called for clarification of procedures for certifying host-vector systems. Others asked that the standards and procedures for future Guideline revisions be explicitly stated. Another wanted procedures that clearly set forth public notice and comment in advance of RAC decisions. And another believed the proposed Guidelines "exacerbate the problems of self-regulation" and urged that "HEW supervise the administration and enforcement of the Guidelines."

One commentator suggested a procedural mechanism for minor or partial revisions. He advised that RAC recommendations be published in the FEDERAL REGISTER for comment, and that the comments be taken into account by the RAC before it forwards final recommendations to the Director. Thus, NIH in these cases would act in

the light of advice reflecting public views.

Another commentator suggested that each time NIH receives an application for an exception to a prohibited experiment, notice be published in the FEDERAL REGISTER, and that after a public comment period, final notice of agency action should also be published there.

**NIH Procedures.** The NIH Guidelines of 1976 provided little or no discretion in their administration or revision. As a result, many recommendations by the RAC could not be accepted because of NIH's lack of authority under those Guidelines to approve them. The revision proposed by the RAC in September 1977 attempted to correct this inflexibility by providing for discretion under specified conditions, with procedures set forth to ensure opportunity for public notice and comment. However, the standards and procedures for exercise of discretionary authority in the proposed revision, as many of the commentators pointed out, needed greater definition and clarity.

The commentators' procedural recommendations provided a focus for the DHEW Committee in its intensive review of these issues in the proposed revisions. Other comments from the scientific community, from many witnesses at the public hearing, and from a DHEW meeting with environmental interest groups augmented the efforts to define avenues for appropriate utilization of NIH authorities. On the basis of the comments made in correspondence and at the September 15 hearing, part IV has been substantially revised to provide for public access and participation in NIH activities under the Guidelines. It clearly sets forth the procedures that will govern the exercise of NIH authority.

First, there is a group of major actions for which the NIH Recombinant DNA Advisory Committee (RAC) will advise the Director after an opportunity for public and Federal agency comment. These actions include lowering or assignment of containment levels where the Director judges the action to be major; certification of new host-vector systems; exceptions to the prohibitions; modification of a list of recombinant DNA sources (microorganisms) to be exempt from the Guidelines and other changes in the Guidelines.

For these major actions the following procedures apply. The Director must seek the advice of the RAC and provide an opportunity for public and Federal agency comment. Specifically, the agenda of the RAC meeting citing the major actions will be published in the FEDERAL REGISTER at least 30 days before the meeting, and the Director will simultaneously publish the pro-



posed actions in the *FEDERAL REGISTER* for comment. In addition, the Director's proposed decision, at his discretion, may be published in the *FEDERAL REGISTER* for 30 days of comment before final action is taken. The Director's final decision, along with response to the comments, will be published in the *FEDERAL REGISTER* and the *Recombinant DNA Technical Bulletin*. The RAC and IBC chairpersons will be notified of this decision.

There is a group of lesser actions for which the RAC will advise the Director after a meeting announced as described above. These actions include all interpretations of determinations referred by ORDA, changes and assignment of containment levels, approval of large-scale experiments for rigorously characterized recombinant DNA where the absence of harmful genes has been established, and designation of certain class 2 agents as class 1 for purposes of the Guidelines. The Director's decision will be transmitted to the RAC and IBC chairpersons and published in the *Recombinant DNA Technical Bulletin*.

And finally, there is a group of administrative and scientific functions in the Office of the Director that may be delegated to the Office of Recombinant DNA Activities (ORDA), involving implementation of the Guidelines and their interpretation. Again, decisions by the Director in these matters will be published in the *Recombinant DNA Technical Bulletin*, and notice will be given to the RAC and IBC.

There was considerable Committee discussion on the standards to guide administrative discretion. It was agreed that the Guidelines should set forth a general standard. Accordingly, they now charge the Director to "with each proposed action, through appropriate analysis and consultation, to determine that it complies with the Guidelines and presents no significant risk to health or the environment." For a discussion of NIH efforts in risk assessment, see part III of this document and the Environmental Impact Assessment (Appendix I).

The Guidelines now reflect these roles and relationships in detail and identify all of the responsibilities in cross-reference on the other sections of the Guidelines and to the Administrative Practices Supplement. As indicated above, opportunities are afforded for public access and participation, with formal procedural requirements based on the significance of the discretionary authority. In light of these procedures, hearings by the Director's Advisory Committee may be unnecessary; but if circumstances warrant, the committee can play an oversight role as it has done in the past.

**Recombinant Advisory Committee Membership.** The correspondents and

witnesses at the September 15 hearing who commented on process considerations also expressed opinions on membership of the Recombinant DNA Advisory Committee (RAC). A number of recommendations were made concerning representation. Some witnesses at the September 15 hearing urged that representatives from the regulatory agencies, such as the Environmental Protection Agency, the Food and Drug Administration, and the Occupational Safety and Health Administration, have full voting membership on the RAC. It was also suggested that a representative from the Council on Environmental Quality serve on the committee. The view was expressed that the representation of these agencies on the Federal Interagency Advisory Committee on Recombinant DNA Research could not substitute for their full participation on the RAC. And it was suggested that representatives from the regulatory agencies constitute a subcommittee of the RAC for purposes of considering all future modifications of part IV.

Some Federal agency commentators suggested that representatives from research agencies such as the National Science Foundation, the Department of Agriculture, and the Veterans Administration serve on the RAC, and perhaps be permitted to consider exceptions to the prohibitions in the Guidelines.

Several commentators recommended that representatives from unions and public interest groups serve on the committee. Quotas for membership were also suggested for public interest groups, unions, and nonprofessional laboratory workers. Public interest members might also be permitted to consider exemptions and exceptions to the prohibitions.

There were a number of recommendations concerning professional and scientific expertise. One commentator advocated representation from "knowledgeable specialists in environmental processes and effects on ecosystems and their biota." Other recommended that the committee include scientists from Federal research agencies, scientists critical of the guidelines, and experts in epidemiology, medical microbiology, and clinical infectious disease research. And finally, it was suggested that RAC be advisory to the Department rather than to NIH.

Many of these concerns were raised at the December 1977 meeting of the Director's Advisory Committee (DAC) by witnesses commenting on the revised Guidelines as proposed by the RAC. As I stated in addressing those concerns in my July 28, Decision, I am acutely aware of the need for broad representation on the RAC, and this

was considered in the selection of new members.

To ensure fairness, however, nominations for openings on the RAC are publicly and widely solicited. In July 1978 a notice was filed in the *FEDERAL REGISTER* requesting public recommendations for RAC membership. All nominations are considered in selecting members of the committee. This open nomination process will be repeated annually, and thus NIH will not be the only source of RAC nominations. Further, nominations are being solicited from all agencies represented on the Federal Interagency Advisory Committee.

There was considerable discussion by the DHEW Committee about the membership of the RAC. The present RAC has 16 members, 2 of whom are lay persons. The DHEW Committee agreed that the composition should reflect the requirements set for the IBCs at the local level. Thus, it is required that at least 20 percent of the RAC members shall be persons knowledgeable about such matters as applicable law, standards of professional conduct and practice, public and occupational health, and environmental safety. In addition, it is recommended that one member be a "nondoctoral" person from a laboratory technical staff.

It was also agreed that the scientific representation on the committee should be broadly based to include persons knowledgeable in recombinant DNA technology and biological safety, but also with expertise in the broader disciplines of biology and medicine—i.e., microbiology, molecular biology, botany, ecology, virology, genetics, infectious disease, plant pathology, and epidemiology.

In view of the expanding role and responsibilities of the RAC, it was though appropriate to augment the expertise and representation. Under a new chapter, the RAC will be expanded to 20 members.

In addition, all Federal agencies represented on the Federal Interagency Advisory Committee will have nonvoting members on the RAC. (At present, some research agencies already have liaison members, such as the National Science Foundation and the Department of Agriculture.) These representatives will be nonvoting because of the large number of Federal agencies involved, but they will be participating members encouraged and enabled to present their agencies' concerns on scientific and other issues.

All members of the RAC may participate on the several subcommittees of the full committee. Thus, there is clearly no need to mandate the nature, structure, or function of subcommittees created by the chairperson in consultation with committee members. Finally, the RAC is advisory to the Sec-



retary of HEW and the Assistant Secretary for Health, as well as to the Director, NIH.

Pending the expansion and restructuring of the RAC, no changes will be made in these Guidelines and no decisions will be made requiring the RAC's prior review and advice.

**Federal Interagency Advisory Committee and Recombinant DNA Research.** A meeting of the Federal Interagency Advisory Committee and Recombinant DNA Research was held on October 12, 1978, to consider agency comments on the proposed revised Guidelines and proposed roles for the committee. Several agency representatives noted that under the discretion granted in the Guidelines, cognizance should be taken of Federal agency roles. Enhancement of the roles for Federal agencies other than NIH was discussed with the committee. This included the proposal of non-voting membership on the RAC, as noted above, and nominations from the agencies for potential voting members. As defined under the new procedures promulgated in part IV, all Federal agencies through their members will have an opportunity to participate in the RAC proceedings and may file written comments concerning RAC activities. Interagency Advisory Committee members will receive RAC agendas and FEDERAL REGISTER notices.

In additions to participating in the proceedings of the RAC, all agencies represented on the Federal Interagency Advisory Committee are now afforded an opportunity to request a meeting of that committee to consider RAC actions in light of their concerns. Some RAC actions, like a recommendation to release recombinant organisms into the environment, will undoubtedly necessitate a meeting of the Interagency Advisory Committee to provide information and seek consensus. Periodic meetings of this committee will also continue to be held for evaluation of recombinant technologies and their regulation under the Guidelines. (For reference, a list of the agencies represented on the Interagency Advisory Committee is presented in Appendix II.)

#### *Scientific Counselors for ORDA*

ORDA will provide consultation to Federal agencies regarding the Guidelines, and a board of scientific counselors from all Federal agencies that support or conduct recombinant DNA work will advise ORDA on the activities of the Office of the Director, ORDA, and the RAC. A key task for the board will be to ensure a common registry of all federally funded recombinant DNA research.

The DHEW Committee expressed the wish that Federal cooperation continue, and strongly endorsed the new

responsibilities of the Federal agencies under the revised Guidelines.

#### **RESPONSIBILITIES OF NIH (SPECIFIC)**

##### *Office of the Director*

The principal issues here relate to the standards and procedures for governing the discretion of the NIH Director under the Guidelines. All of the responsibilities that the Guidelines assign to the Director are now grouped under "general responsibilities" (for promulgating rules and overseeing implementation of the Guidelines) and "specific responsibilities," which include the opportunity for public and Federal agency comments. This new organization clearly delineates the responsibilities and the procedures and standards to govern the exercise of discretion based on the advice of the RAC and ORDA.

The DHEW Committee discussed the need for periodic review and assessment of NIH's experience in conducting and supporting recombinant DNA research. Accordingly, it was agreed that appropriate language should be inserted in the Guidelines that the Director, at the end of 36 months from their implementation, will report on the Guidelines and NIH experience under them in consultation with the RAC and the Federal Interagency Committee. He will solicit public comment on the draft before transmitting the final report with response to comments to the Assistant Secretary for Health and the Secretary, HEW.

In addition, the Director is now responsible for supporting training programs in laboratory safety for IBC members, Biological Safety Officers, Principal Investigators, and laboratory staff.

##### *Recombinant Advisory Committee*

A major concern of the witnesses at the September 15 hearing, and of the commentators on the proposed revised Guidelines, was related to the composition of the RAC, as discussed above. The new procedures clearly guide the discretion of the committee and provide for full public and Federal agency participation. The responsibilities of the RAC have been enhanced, with full access to the public and the Federal agencies. As I stated in my Decision of July 1978 accompanying the proposed Guidelines, the task for all RAC members has been enormous and their work and spirit of cooperation have been exemplary. I look forward to continued cooperation with Dr. Jane Setlow, Chairman, and all of the committee members. Their assistance is vital to the integrity of this research under the Guidelines.

#### *Office of Recombinant DNA Activities*

The majority of comments concerning ORDA focused on the office's oversight responsibility. The issues concerning delegation of authority to the IBC's and the role of ORDA in registering not only recombinant DNA activities but other data relating to health surveillance have been discussed in the previous section on local institutions.

There were several comments concerning the need for increased staffing for ORDA to meet the new responsibilities under the Guidelines. Additional staff has been provided, and there will be need for more in light of the new responsibilities of the Recombinant Advisory Committee to solicit public and Federal agencies' comments.

As noted previously in the section on the Interagency Committee, a board of scientific counselors from the other Federal agencies that conduct or support recombinant DNA research will be established as advisory to ORDA. This board is created in response to suggestions from Federal agencies for some mechanism to ensure uniformity in interpretations and determinations made under the Guidelines where discretion is granted. An early task of the board will be to assist in creating and maintaining a registry for all recombinant DNA activities funded by the Federal Government. The board will also assist ORDA's Director in forwarding to the RAC all requests from other Federal research agencies for action on such matters as certification of new host-vector systems. We are, in fact, trying to ensure a capability for uniform interpretation and implementation of the Guidelines throughout the Federal sector.

Another commentator urged that a time-frame be set for implementing the new standards and procedures. This request is a most important one. In anticipation of the release of the Guidelines, procedures have been drawn up for meeting the new requirements. Dr. William Gartland, Director of ORDA, has sent a letter to all institutions, IBC chairmen, and Principal Investigators, specifying the measures to be taken within the next three months to implement the new Guidelines effectively.

**Registration.** Here the principal comments came from the Federal agencies and private industry. The proposed revised Guidelines require the institutions that receive NIH funds for recombinant DNA research to register all recombinant DNA projects, irrespective of the source of funding. Representatives from Federal research agencies pointed out that institutions should not be required to register with NIH if they are already registering with the Federal agency that supports the work. Accordingly,



## NOTICES

the Guidelines now specify that an institution need not register with NIH its projects funded by another Federal agency when that agency maintains a registry and provides the NIH with essential information. The institution will register projects directly with NIH if the supporting Federal agency does not choose to maintain its own registry.

At a meeting held with the DHEW Committee, representatives of the Pharmaceutical Manufacturers Association urged greater protection for proprietary and patent information under the Guidelines. The proposed revised Guidelines offered a system of voluntary registration and certification for the private sector which was not available under the 1976 Guidelines. In addition, a representative from the Commerce Department also urged expansion of the Guidelines to protect proprietary and patent information. On the other hand, environmental interest groups have expressed concern that there be maximum disclosure of information. Because of the complexity of the issue, and the general perception that NIH does not have the powers to completely protect proprietary rights and trade secrets, this aspect of the Guidelines will be handled separately after their issuance. The Food and Drug Administration is now considering issuing regulations that would require drug companies to comply with the NIH Guidelines.

**Compliance.** Several of the commentators and witnesses at the September 15 hearing recommended stronger language in the Guidelines concerning compliance with the Guideline provisions. The proposed revision stated that noncompliance may result in suspension, limitation, or termination of financial assistance. Several commentators urged that the language be made mandatory. Others suggested that possible violations be ranked, with definite penalties set in each case, including criminal penalties. Still others urged invocation of Section 361 of the PHS Act to ensure compliance through regulation.

Many of these issues were raised at the December hearing of the Director's Advisory Committee and in correspondence on the Guidelines as proposed by the RAC. In response to the suggestions, a section on compliance was included in the proposed revision. However, as I noted in my Decision accompanying that publication, NIH has no authority to impose fines in the absence of new legislation. I also noted that appropriate HEW procedures will be followed should suspension or termination of a grant be necessary. In light of the lack of statutory authority, penalties for negligence and criminal penalties should not be specified. It has been suggested that NIH might

seek reimbursement for any funds expended upon activities not conducted in accordance with contractual assurances. This recommendation differs from current HEW grant policy and will require much more consideration.

On the basis of DHEW Committee discussion, a new provision will allow NIH to require prior approval of any and all recombinant DNA research projects if the institution fails to comply with the Guidelines.

Invocation of Section 361 of the Public Health Act has been carefully considered by the Interagency Committee and the Department over the past two years. The most recent expression of interest in this authority was in a letter six Senators requesting Secretary Califano to consider invoking Section 361 to regulate recombinant DNA research. The letter and the Secretary's response are included in Appendix III to this Decision. Briefly, the Secretary said that the Department does not intend to evoke existing statutory authorities to regulate recombinant DNA activities at this time. He went on to quote the Interagency Committee's report of March 15, 1977, dealing with elements for legislation, including the determination that Section 361 would require a reasonable basis for concluding that recombinant DNA research may cause human disease. Such a conclusion is tenuous at best and would at present be an inappropriate basis for invoking the regulation. The Secretary, however, noted in his letter that if the Department had to act speedily, Section 361 is available and would be used. In the Secretary's view, only legislation would justify establishing regulations.

## V. FOOTNOTES AND REFERENCES

In reply to correspondents' suggestions and NIH review, minor changes have been made in Footnotes 3 and 5; and five new footnotes—2A, 19A, 33A, 33B, and 37A—have been added.

A correspondent recommended that text be added to Footnote 2 to discuss the basis for allowing cloning of genetic information from *Vesicular stomatitis virus* and moderate-risk oncogenic viruses. Since Footnote 2 already refers the reader to the July 28, 1978, Decision document, where this is discussed in detail, no further discussion in Footnote 2 seems necessary.

## APPENDIX A

(Director's Decision concerning Appendix A of the Guidelines)

There were many comments concerning the list of exchangers in Appendix A to be exempted from the Guidelines under Exemption I-E-4.

Some correspondents recommended additions to the list, including *Caulobacter crescentus*, *Agrobacterium*, *Proteus*, and *Xanthomonas*.

On the other hand, some correspondents felt that there was insufficient documentation for the entries on the list and that the list should be by species, not genus.

One correspondent recommended citing Bergey's *Manual of Determinative Bacteriology*. Another wrote, "It is also questionable why one should list *Escherichia coli* exchangers and not others in nature such as the organisms that exchange with *Bacillus subtilis*, with *Haemophilus influenzae*, with *Neisseria gonorrhoeae*, etc."

In response to the many comments received, the list of organisms to be exempt from the Guidelines under Exemption I-E-4 has been carefully reconsidered. The discussion below attempts to make more explicit the considerations used in constructing this list. In addition, the criteria for inclusion on the list have been tightened, reducing the list considerably and thus exempting fewer experiments from the Guidelines. References supporting the entries to the list are given below (refs. 1-22). The final list (Appendix A) closely resembles the "first list" described in Appendix D to the July 28, 1978, Environmental Impact Assessment.

It should be emphasized that the evolution of this list will continue as more experiments are done and as we gain more knowledge in this rapidly advancing field. In addition, other organisms recommended by some of the commentators (*Bacillus* or *Haemophilus* species, for instance) are currently being considered by the RAC for future inclusion under this exemption.

As noted in Appendix D to the July 23, 1978, Environmental Impact Assessment: "The natural transfer of genes between bacteria occurs by transduction (bacterial virus-mediated), transformation (uptake of isolated DNA by a bacterial cell), or conjugation (plasmid-mediated transfer of genes between bacteria requiring cell-to-cell contact). A reasonable generalization is that virtually all closely related species of bacteria can exchange genes by transduction and transformation, the former limited by the relatively narrow host-range of transducing bacteriophage and the latter by the requirement, in the case of chromosomal DNA, for homology of DNA in most recombination events. Conjugal mating with exchange of DNA can occur between virtually all Gram-negative bacteria, including naturally occurring soil and intestinal species, when mediated by a plasmid of broad host-range (for example, the Inc P-1 group plasmids). Recently, conjugal mating has also been shown to occur between strains of certain species of *Streptococcus*, a Gram-positive organism (for example, *Streptococcus faecalis*). To date, however, conjugal mating has not been demonstrated between Gram-negative and Gram-positive bacteria."

"The relatedness of different microbial species can be estimated by determining the extent of DNA homology between them or by studying the properties of different microorganisms in genetic crosses. As a general rule, organisms that show considerable homology of their nucleotide sequences under a standard set of experimental conditions have the capacity to mutually integrate chromosomal genes. For example, in the case of the *Enterobacteriaceae* family of bacteria (includes *Escherichia coli* K-12), there is both extensive DNA-DNA homology (1) and chromosomal gene exchange (2) with a reasonable correlation between the degree of DNA-DNA homology and the capacity to mutually integrate chromosomal genes."

"Genetic relatedness, as indicated by a high level of DNA-DNA homology between different microorganisms, is not, however,



an absolute requirement for the exchange of chromosomal genes between bacteria. In fact chromosomal gene transfer among diverse members of the Gram-negative group of bacteria has been demonstrated where the microorganisms involved show little or no DNA-DNA homology. In these cases the exchange of chromosomal genes is promoted by a broad-host-range plasmid of the Inc P-1 incompatibility type. These plasmids mobilize the chromosomes of a wide variety of Gram-negative bacteria, incorporate segments of these chromosomes, and are capable of establishing themselves along with covalently linked chromosomal genes in a wide range of Gram-negative bacteria. (3)"

In evaluating a pair of organisms for inclusion as nonnovel exchangers, we are making an estimate of the probability that the combination of genes might have occurred naturally. If the combination is not a new one, then there should be no special hazard in creating such an organism by recombinant DNA technology. Thus we can exempt this combination from the Guidelines.

Any conclusion about exchange between organisms involves some extrapolation from the experimental data available. We have tried, in the discussion below, to make explicit these extrapolations and the scientific bases for making them. For this purpose, the types of criteria which might be taken into account in preparing a list of exchangers are divided into four categories. The first two were those used in constructing Appendix A in these final revised guidelines. The first three were used in constructing the version of Appendix A which appeared in the July 28, 1978, proposed revised guidelines. All four were used in constructing a list approved by the RAC and described as the "third list" in Appendix D to the July 28, 1978, Environmental Impact Assessment.

1. *Organisms which exchange chromosomal genetic information which becomes stably integrated into the host chromosome.* This, the most stringent criterion for exchange, requires significant homology between recombining segments. Organisms which meet these criteria will therefore be closely related by DNA homology measurements (Ref. 1, 2). In addition, more than one mechanism of genetic exchange may be found (i.e., transduction and plasmid mobilization), and transfer of many different markers may be demonstrated. The major extrapolation involved in this category is the extension of data from one strain to others in the same species or genus. In the Appendix A list, most of the entries are listed as genera (*Shigella*, *Salmonella*, etc.), while the *Pseudomonas aeruginosa* species is listed. One can generalize from species to genus when there is evidence that all members of the genus behave similarly, and show extensive DNA homology. In addition, in some cases, exchange has been demonstrated in many species of the genus. The DNA homology test is convincing for *Shigella*, but not for *Pseudomonas*.

2. *Organisms which exchange chromosomal information that is not necessarily integrated into the chromosome of the recipient (for instance, transfer via F or R).* This sort of exchange can occur in the absence of extensive DNA homology between the organisms, and requires only that the plasmid and its chromosomal genes be maintained in the recipient organism.

Although two organisms meeting these criteria might not be closely related, this

type of exchange is probably the best model of a recombinant DNA experiment. In both cases, relatively small amounts of genetic information are transferred, usually in plasmid form, to an otherwise "foreign" genetic background. Therefore, it seems reasonable to accept evidence of such exchange as grounds for exemption.

Criteria 3 and 4 deal specifically with Inc P-1 plasmids, but the principles can be extended to other exchange mechanisms.

3. *Organisms which show evidence of a plausible mechanism for exchange (e.g., R<sup>+</sup> formation or evidence of mobilization of chromosomal genes by an Inc P-1 plasmid.)* In this case, the plasmid itself has been shown to move from organism to organism. It has been shown to pick up chromosomal genes, but the transfer of these chromosomal genes in interspecies matings has not necessarily been demonstrated.

To endorse these criteria, we must extrapolate from the transfer within the species to more distantly related organisms. For such an extrapolation, one must assume that no barriers will exist for R<sup>+</sup> transfer that do not exist for transfer of the plasmid itself. In many tested cases, this is clearly true: transfer of chromosomal genes incorporated into an R factor is comparable in frequency to transfer of the plasmid itself, and the R<sup>+</sup> can be moved to a broad range of organisms (4). However, this may not be universally true (5).

4. *Organisms which can receive or donate broad host range plasmids.* Since these plasmids are known, in many cases, to mobilize the chromosome and transfer chromosomal genes, such transfer might be expected for any organism that receives or donates the plasmid. This extrapolation assumes that (i) chromosomal pickup is always able to occur with these plasmids and (ii) transfer of chromosomal genes to other species will occur (this latter case is the same as that analyzed under criterion 3).

Analysis of the basis for the first extrapolation would include consideration of the numerous cases where such mobilization and transfer can be detected (see, for instance, ref. 5-10) and those few where it cannot (11).

It is my decision that the data supporting the use of criteria 3 and 4, while suggestive, are not yet compelling enough to warrant exemption from the Guidelines for recombinant DNA experiments. As more data are accumulated, this conclusion will be carefully reconsidered.

#### The Issue of Two-Way Exchange

The organisms listed in appendix A fit the first two criteria described above—i.e., in all cases, there is direct evidence of chromosomal exchange between two species on the list, and many show extensive DNA homology as well. In addition, for all the organisms on this list, exchange can be demonstrated in two directions. Further, if organisms A and B both exchange genetic information (both donate and receive) with a third organism—*E. coli* K-12, for instance—then *E. coli* K-12 can act as a path for the DNA of organism A to reach B, and vice versa. Thus, the requirement for two-way exchange allows us to exempt recombinants made between A and B. Therefore, we have exempted "any recombinant DNA molecules that are (1) composed entirely of DNA segments from one or more of the organisms listed below and (2) to be propagated in any of the organisms listed below."

It would make sense, of course, to have one-way lists as well, where cloning exempt from the Guidelines would only be allowed in the recipient. The creation of such lists will be considered by the RAC.

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## APPENDIX B

(Director's Decision concerning Appendix B of the Guidelines)

Three correspondents correctly point out that since the publication in 1974 of the "CDC Classification of Etiologic Agents on the Basis of Hazard" (which is repeated verbatim as Appendix B to the Guidelines), *Actinomyces* have been reclassified. Formerly considered to be fungal agents, they are now considered bacterial agents. An explanatory footnote has been added to the table.

## APPENDIX I—ENVIRONMENTAL IMPACT ASSESSMENT

## ENVIRONMENTAL IMPACT OF THE FINAL GUIDELINES

An *Environmental Impact Assessment of the NIH-Proposed Revised Guidelines (EIA)* was published with the Guidelines in the *FEDERAL REGISTER* of July 28, 1978. The assessment was based on an intensive analysis of the Guidelines then in effect, the Guidelines as proposed by the Recombinant DNA Advisory Committee in September 1977, and the Guidelines as proposed by NIH in July 1978. The conclusion of the assessment was that there would be no adverse impact of the NIH-proposed changes upon the environment.

The issues raised by the commentators in correspondence and by the witnesses of the September 15 hearing on the NIH-proposed revised Guidelines are reviewed in detail in the accompanying Decision document. It is the conclusion, based on that review of the alternatives proposed in July 1978 and the decisions reflected in the final Guidelines, that there will be no adverse impact of the Federal actions upon the environment. Indeed, in the extensive revision of part IV, these final Guidelines enhance public participation and accessibility at the national and local levels, with increased emphasis on health surveillance and safety training. The final Guidelines provide an even stronger framework to ensure that no significant risk is presented to the public health or the environment.

Consideration now follows of certain issues relating to the EIA of July 28,

1978, which were raised in correspondence and by witnesses at the September 15 hearing.

## NEPA Considerations

A witness at the September 15 hearing cited the EIA as being inadequate and held that a full Environmental Impact Statement (EIS) should be prepared. The witness stated that an EIS is clearly required by the law. In addition, the witness found the EIA inadequate in its analysis of the revisions in such areas as exemptions and the use of *E. Coli* K-12 and other host-vector systems.

In our view, the EIA prepared by NIH on the proposed revisions to the NIH Guidelines fully satisfies the requirements of the National Environmental Policy Act of 1969 (NEPA).

The current Guidelines on Recombinant DNA Research were issued on June 23, 1976, and published in the *FEDERAL REGISTER* on July 7, 1976 (41 F.R. 27902). They were developed by NIH after opportunity for public comment and an open meeting at which members of the public were invited to testify (41 F.R. 2105).

In the Decision of the Director, NIH, which accompanied the 1976 Guidelines, it was indicated that NIH would prepare a draft EIS on the Guidelines in order to give the public further opportunity to comment. The draft EIS was published in the *FEDERAL REGISTER* on September 9, 1976, with a preamble soliciting public comment (41 F.R. 38426). After the close of the comment period, a final EIS was prepared, taking into account the comments received and scientific developments up to that time. The EIS actually became final on November 28, 1977, when notice of its receipt was published in the *FEDERAL REGISTER* by the Council on Environmental Quality (42 F.R. 60588).

During this period, scientific evidence has been accumulating that the risks presented by recombinant DNA research, which has always been purely speculative, were indeed remote. As a result, it became apparent that the restrictions in the Guidelines were more stringent than necessary and that the Guidelines needed to be revised. The process of revision was first undertaken by NIH's Recombinant DNA Advisory Committee (RAC), which referred a proposal for revision to the Director, NIH, in September 1977. On September 27, 1977, the Director published the RAC's proposal in the *FEDERAL REGISTER* for public comment (42 F.R. 49596). At the same time, and in a subsequent *FEDERAL REGISTER* notice (42 F.R. 59918), the Director announced a two-day meeting to secure public testimony on the RAC proposal. This meeting was held on December 15-16, 1977, and

witnesses appeared from environmental groups, the scientific community, and industry.

Based on the comments received and the testimony at the December meeting, the Director developed an NIH-proposed revision of the Guidelines (referred to herein as the PRG), relying in part on the RAC proposal. The PRG was issued by the Director, as a proposal, with the approval of the Secretary, on July 19, 1978, and published in the *FEDERAL REGISTER* on July 28, 1978 (43 FR 33042), the preamble to the PRG requested public comment, announced that a further hearing on the PRG would be conducted on September 15, 1978, before an HEW panel chaired by the General Counsel, and indicated that final action on the PRG would be taken after the panel had reviewed both the written comments and those provided at the hearing.\*

When the PRG was published on July 28, it was accompanied by a detailed EIA, which included a discussion of the risks and benefits of recombinant DNA research and an analysis of the current Guidelines, of alternatives to the Guidelines, and of NIH's PRG. In addition to an overall assessment of the environmental impact of the PRG, separate environmental impact analyses were made of each section. The conclusions reached were summarized at the beginning of the EIA as follows:

As can best be determined from all evidence compiled to date and analyzed in numerous scientific and public forums, there will be no adverse environmental impact from recombinant DNA research conducted under the Director's proposed revisions. The Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, issued in October 1977, predicted that the environmental impact of research conducted under the 1976 NIH Guidelines would be the continued protection of the laboratory worker, the general public, and the environment from conjectural hazards. So far, this prediction has been confirmed: We know of no scientists conducting recombinant DNA research in the United States or other countries who are not following the NIH or comparable guidelines, and no untoward effect of the research has been reported. Meanwhile, new scientific evidence as well as extensive experience in operating under the NIH Guidelines indicate that revisions are in order. The predictable effect of continued use of recombinant DNA techniques under the Director's proposed revisions would be a greater realization of the benefits of this valuable tool without compromise of safety. (43 FR 33096).

The EIA prepared by NIH on the PRG discusses in detail scientific developments regarding recombinant DNA research. It justifies the changes proposed by NIH, explains why some RAC and public proposals were not ac-

\* More than 30 persons from environmental groups and the scientific community testified at the September 15 hearing.



cepted, and assesses at some length the anticipated environmental effects of the changes NIH proposed to make.

In my view the EIA represents a conscientious, thoughtful, and thorough effort to carry out our responsibilities under NEPA. As one correspondent noted, the assessment is a "thorough and fully documented analysis . . . that describes the technical aspects of this research and its conjectural risks and benefits." The EIA took a "hard look" at the current Guidelines, the various alternatives, and the environmental implications of the proposed changes. By soliciting public comment and conducting a public hearing, relevant areas of environmental concern were identified. I believe that a convincing case is made in the EIA that the proposed changes would have no significant environmental impact.

My Decision accompanying these final Guidelines reviews at some length exemptions from the Guidelines in light of the comments made by correspondents and witnesses. And indeed, a lengthy analysis of the list of exempt organisms in Appendix A documents the prudence and caution in which NIH is proceeding. On the basis of comments, the list has been modified and the scope of experiments restricted.

It was also asserted by witnesses that the filing of an EIS would provide for public input in the Government's decisions affecting the environment. In my view, NIH's overall response to the issues raised by recombinant DNA research has been to ensure a full public hearing of all issues. When these issues first arose, NIH conducted public hearings, solicited public comment, developed Guidelines, and published an EIS, which ultimately received judicial approval.

Since that time scientific evidence has shown that the initial concerns about the hazards of this research may have been exaggerated. Accordingly, we proposed to relax some aspects of the Guidelines. In doing so, we again conducted hearings and solicited public comment. And the NIH-proposed revised Guidelines were published for comment, followed by a hearing under the aegis of a DHEW committee chaired by Peter Libassi, the DHEW General Counsel. In addition, all of the proceedings and all documents have been published in an ongoing series of volumes that document the basis for NIH policies. The documents contain relevant proceedings of the executive, legislative, and judicial branches. A fourth volume will be published in January containing the transcript of the September 15, 1978, hearing, all correspondence received by NIH commenting on the proposed Guidelines of July 28, 1978, and all other relevant documents.

#### RISK ASSESSMENT

Several witnesses raised issues concerning the concepts of risk and safety as outlined in the Environmental Impact Assessment (EIA). One witness emphasized the concept of risk as "a relatively objective measurement of hazards" and safety as "a subjective expression of the level of risk which is acceptable to a population." He believes the NIH Guidelines and Assessment confuse these two concepts. The Guidelines, in his view, do not provide adequate institutional mechanisms to ensure that the value issues involved in safety are thoroughly aired by the general public. Thus, because safety is "value-laden, subjective, and in a sense, political," the Guidelines must reflect these values by ensuring adequate mechanisms for determining safety standards and their implementation.

The October 1977 EIS on the original NIH Guidelines and the July 1978 EIA on the proposed revisions address in great detail occupational and environmental health and safety concerns. As noted in the EIA (FEDERAL REGISTER, p. 33131, middle column), several changes are proposed in the revised Guidelines "in the implementation, review, and monitoring of recombinant DNA activities at the local and national levels, to insure appropriate safety practices and procedures that would minimize any significant environmental impact."

These modifications focus on a restructuring of roles and responsibilities. The applicability of the Guidelines has been extended to all recombinant DNA research at institutions that receive any recombinant DNA research support from NIH. Biosafety committees have been given broader responsibilities. At the request of several commentators, Appendix D to the original Guidelines has been revised and updated as *Laboratory Safety Monograph—A Supplement to the NIH Guidelines*. The monograph is a compendium of useful safety information, including instructions on emergency procedures, laboratory techniques for biohazard control, and decontamination and disposal methods. It provides much detail on the responsibilities of the local institution for safety practices and procedures. The impact of these actions and the restructuring of part IV of the Guidelines will be the promotion of safer conduct of this research, affording a greater measure of protection to the environment, with emphasis on occupational health and safety.

Several commentators also urged NIH to initiate and fund a comprehensive risk-assessment program to provide a scientific basis for defining appropriate containment requirements for recombinant DNA experiments.

The DHEW Committee reviewed NIH efforts in this regard. It was noted that recombinant DNA research experiments provide a great deal of information on risks. In addition, NIH is supporting a number of studies in risk assessment. The participants at the Falmouth Conference\* recommend studies in six areas, and NIH is following up on those recommendations.

The Rowe-Martin polyoma experiments are discussed in the Decision Document. In addition, intramural NIH scientists are collaborating with scientists from other institutions in testing the virulence in mice of *E. coli* K-12 containing "shotgun clones" of recombinant DNA derived from other species.

A number of contractors of the National Institute of Allergy and Infectious Diseases are testing the biological containment capabilities of various derivatives of *E. coli* K-12. Some are testing the survival and capacity of plasmid and phase vectors to be transmitted to secondary bacterial hosts in the gastrointestinal tract of man and mouse. Others are assessing these parameters in model sewage treatment systems and in situations simulating accidental spills and other types of accidental release of the organisms for experimental procedures.

In addition, investigators proposing systems to be certified by NIH as HV1 or HV2 must perform certain specified tests on these systems relevant to their survival and transmission properties. It is also anticipated that if investigators seek exceptions to the prohibitions for specified clones, NIH will request substantial risk-assessment experiments to be performed to evaluate claims of safety.

Another commentator noted that Dr. Sidney Brenner of the Medical Research Council's Laboratory for Molecular Biology in Cambridge, England, had stated that he believed the whole method of risk-assessment up to now is "fragmentary" and that what is needed is a "more systematic approach," which he was trying to take. Dr. Brenner, when asked for more information on his studies, explained that the method of risk-assessment he referred to is not a new experimental approach but a new analytical approach. Dr. Brenner's work will be followed closely for any new information that sheds light on potential risks or safety of experiments under the Guidelines.

#### SOCIAL ETHICS

A witness at the September 15th hearing noted that "the steps taken to insure containment are of great immediate importance and the present guidelines should be continued." But

\*See Journal of Infectious Diseases, 137:704-708, May 1978



## NOTICES

he stated that "ultimately the discussion, kinds of facility and guidelines are simply irrelevant." In his view, human security may be threatened by "the biologic revolution." He notes that just as the "nuclear reality" has led to the term "omnicide," and environmental pollution to "ecocide," biological research may lead to "genecide."

As noted in my Decision document (FEDERAL REGISTER, July 28, 1978), NIH has been asked to provide a forum for dealing with social issues relating to "genetic engineering." The concerns of this witness may be taken in the same context. My Decision notes that NIH has been addressing the policy questions involving the safety of this research, not the "potential future application \* \* \* to the altering of the genetic character of higher forms of life, including man \* \* \*." In light of public concern, a study is warranted of the ethical, legal, and social implications of these techniques. The National Commission for Protection of Human Subjects of Biomedical and Behavioral Research considered, but was unable to initiate, a study \* \* \*." Such a study might be considered by the Department's newly created Ethical Advisory Board. It could also be a key priority for the National Commission for the Protection of Human Subjects, which was reauthorized by the Congress before adjournment of this session.

#### APPENDIX II—FEDERAL INTERAGENCY ADVISORY COMMITTEE ON RECOMBINANT DNA RESEARCH, OCTOBER 1978

##### DEPARTMENT OF AGRICULTURE

Dr. James Nielson, Deputy Assistant Secretary for Conservation, Research, and Education, U.S. Department of Agriculture, Washington, D.C. 20250.  
Charles F. Lewis, Ph. D. (Alt.), Staff Scientist, Plant and Entomological Sciences, National Program Staff, ARS, USDA, BARC-West, Beltsville, Maryland 20705.  
Dr. Clarence O. Grogan (Alt.), Principal Agronomist, Conservation, Research, and Education, U.S. Department of Agriculture, Washington, D.C. 20250.

##### DEPARTMENT OF COMMERCE

Jordan J. Baruch, Sc. D., Assistant Secretary for Science and Technology, U.S. Department of Commerce, Washington, D.C. 20230.

##### DEPARTMENT OF DEFENSE

William R. Beisel, M.D., Scientific Adviser, U.S. Army Medical Research Institute of Infectious Diseases, Ft. Detrick, Frederick, Maryland 21701.

##### DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Lowell T. Harmison, Ph. D., Science Adviser, Officer of Health Policy, Research, and Statistics, OASH, Parklawn Building, Room 17A-55, Rockville, Maryland 20857.

##### CENTER FOR DISEASE CONTROL

John H. Richardson, D.V.M., Director, Office of Biosafety, Center for Disease Control, Atlanta, Georgia 30333.  
Anthony Robbins, M.D., Director, National Institute for Occupational Safety and Health, Parklawn Building, Room 8-05, Rockville, Maryland 20857.

##### FOOD AND DRUG ADMINISTRATION

Robert L. Elder, Sc. D., Deputy Associate Commissioner for Science, Food and Drug Administration, Parklawn Building, Room 14-57, Rockville, Maryland 20857.  
Rosa M. Gryder, Ph. D. (Alt.), Staff Science Adviser, Office of Science, Food and Drug Administration, Parklawn Building, Room 7-83, Rockville, Maryland 20857.  
John C. Petricciani, M.D., Deputy Director, Division of Pathology, Bureau of Biologics, FDA, NIH Building 29, Room 514, Bethesda, Maryland 20014.

##### DEPARTMENT OF ENERGY

James L. Liverman, Ph. D., Deputy Assistant Secretary for Environment, Department of Energy, Washington, D.C. 20545.  
Charles E. Carter, M.D. (Alt.), Manager, Biomedical Programs, Office of Health and Environmental Research, Department of Energy, Washington, D.C. 20545.  
Walter H. Weyzen, M.D. (Alt.), Manager, Human Health Studies Programs, Office of Health and Environmental Research, Department of Energy, Washington, D.C. 20545.

##### DEPARTMENT OF INTERIOR

Mariano Pimentel, M.D., Medical Director, Department of Interior, 18th and C Streets, NW., Room 7045, Washington, D.C. 20240.

##### DEPARTMENT OF JUSTICE

Mr. Anthony Liotta, Deputy Assistant Attorney General, Land and Natural Resources Division, Department of Justice, Washington, D.C. 20530.

##### DEPARTMENT OF LABOR

Eula Bingham, Ph. D., Assistant Secretary for Occupational Safety and Health, Department of Labor, Washington, D.C. 20210.

##### DEPARTMENT OF STATE

Mr. William J. Walsh III, Biomedical Research Liaison and Health Affairs Officer, Bureau of Oceans and International Environmental and Scientific Affairs, Department of State, Washington, D.C. 20520.

##### DEPARTMENT OF TRANSPORTATION

Mr. Douglas A. Crockett, Department of Transportation, Trans Point Building, Room 6405, 2100 Second Street SW., Washington, D.C. 20590.

##### ENVIRONMENTAL PROTECTION AGENCY

Thomas A. Murphy, Ph. D., Acting Deputy Assistant Administrator for Health and Ecological Effects, Environmental Protection Agency, 401 M Street, SW., Washington, D.C. 20460.

##### EXECUTIVE OFFICE OF THE PRESIDENT

Gilbert S. Omenn, M.D., Ph. D., Assistant Director for Human Resources, Office of Science and Technology Policy, Old Ex-

ecutive Office Building, Room 360, Washington, D.C. 20500.

Mrs. Carroll L. Bastian, Senior Staff Member for Environmental Health and Toxic Substances, Council on Environmental Quality, 722 Jackson Place, NW., Washington, D.C. 20006.

##### NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

David L. Winter, M.D., Director for Life Sciences, National Aeronautics and Space Administration, 400 Maryland Avenue SW., Room 5111, Washington, D.C. 20546.

##### NATIONAL SCIENCE FOUNDATION

Herman W. Lewis, Ph. D., Section Head of Cellular Biology, Division of Physiology, Cellular, and Molecular Biology, National Science Foundation, Washington, D.C. 20550.  
Philip D. Harriman, Ph. D., Program Director of Genetic Biology, National Science Foundation, Washington, D.C. 20550.

##### NUCLEAR REGULATORY COMMISSION

Mr. Frank Swanberg, Jr., Chief, Health, and Environmental Research Branch, Nuclear Regulatory Commission, Washington, D.C. 20555.

##### U.S. ARMS CONTROL AND DISARMAMENT AGENCY

Robert Mikulak, Ph. D., Physical Science Officer, Multilateral Affairs/Advanced Technology, U.S. Arms Control and Disarmament Agency, Washington, D.C. 20451.

##### VETERANS' ADMINISTRATION

Jane S. Schultz, Ph. D., Chief, Program Review Division, Veterans' Administration Central Office, 810 Vermont Avenue, NW., Room 755, Washington, D.C. 20420.

##### CHAIRMAN OF THE COMMITTEE

Donald S. Fredrickson, M.D., Director, National Institutes of Health, Bethesda, Maryland 20814.

##### EXECUTIVE SECRETARY OF THE COMMITTEE

Joseph G. Perpich, M.D., J.D., Associate Director for Program Planning and Evaluation, National Institutes of Health, Bethesda, Maryland 20814.

#### APPENDIX III

##### EXCHANGE OF LETTERS BETWEEN SENATORS AND SECRETARY CALIFANO

*[Letter to Senator Kennedy attached; similar letters were sent to the five other Senators]*

UNITED STATES SENATE,  
Washington, D.C., June 1, 1978

Hon. JOSEPH A. CALIFANO, JR.,  
Secretary of Health, Education and Welfare,  
Department of Health, Education and Welfare, Washington, D.C. 20201.

DEAR MR. SECRETARY: Since 1976 four committees of the House and Senate have held nine series of hearings to consider the issues relating to recombinant DNA research. These extended and thorough inquiries have shown that, with respect to the research they support and conduct, the National Institutes of Health have taken a properly cautious approach by prohibiting certain presumably hazardous experiments, requiring certification of the safety of host-vector systems, prescribing physical and biological containment measures for the con-



duct of permissible experiments, and providing for changes in these restrictions as further scientific evidence resolves the uncertainties about the health and environmental effects of using recombinant DNA techniques.

Evidence accumulated in the past year, rather than revealing any hazards associated with these experiments, points to a high level of safety in the use of the predominant host organism, the K-12 strain of *E. coli*. The NIH Recombinant DNA Molecule Program Advisory Committee has recommended changes in the Institute's research guidelines to reflect this evidence, and these recommendations are being considered by Director Fredrickson. Other hosts and vectors have received less scrutiny, and uncertainty remains about risks that may be associated with future applications of the technology. These uncertainties justify continuing to require certain precautions in recombinant DNA work.

However, the hearings have also underscored the need to correct deficiencies in the present system of regulation. Privately supported research activities are not subject to monitoring by NIH nor to sanctions for failure to comply with the guidelines. Application of the NIH standards by other Federal agencies is voluntary. As Director Fredrickson has stated on several occasions, it is doubtful this enforcement by the principal Federal sponsor of recombinant DNA research—NIH—is appropriate. Procedures for revising the standards and exempting certain experiments should be clarified. It is important to ensure the accountability of institutions and investigators, particularly if they are to assume greater responsibility for monitoring compliance. The Federal Government should anticipate commercial applications of recombinant DNA techniques and the concerns they are likely to raise.

In view of these developments and in view of the heavy legislative schedule of the Senate and the Human Resources Committee, we are writing to inquire whether the deficiencies in the present regulatory system can be remedied through executive action in the event final agreement on legislation is not possible. Specifically, it would seem possible to shift monitoring and enforcement responsibilities from NIH to a more appropriate agency within the Department of Health, Education, and Welfare. It would also seem possible to remedy the problems of accountability and of coverage in the process of revising the recombinant DNA guidelines. On the basis of the survey of existing statutory authorities conducted by the Committee on Commerce, Science and Transportation, there seems to be adequate authority to regulate the commercial application of products developed through recombinant DNA technology. There is, however, need for more effective coordination among Federal agencies in the implementation of these authorities.

In this regard, you expressed to Senator Stevenson in your letter of February 27, 1978, that the Food and Drug Administration "... could, under existing authority, require any firm seeking approval of a product which may be the end product of recombinant DNA research to certify to the Agency that it has complied with the NIH guidelines on recombinant DNA." You noted also that FDA has authority to inspect firms making such certification to assure compliance with the NIH guidelines. This statement is important because most,

if not all, recombinant DNA research by the private sector is being conducted by pharmaceutical companies with the objective of developing products that would be marketed in accordance with FDA regulations. A decision by the Administration to use this existing authority would bring the large majority of privately funded recombinant DNA research activities under the NIH guidelines. Is the Administration prepared to use the authority cited in your February 27th letter?

Finally, it has been suggested that section 361 of the Public Health Service Act provides sufficient authority to promulgate regulations covering recombinant DNA research conducted by the private sector with non-Federal funds. Although you have expressed the view that specific legislative authority is preferable to using the authority of section 361, we are raising the issue again for three reasons: (1) The need for new legislation is less clear than it was one year ago when the initial bills were introduced, (2) the existing regulatory deficiencies relating to Federally-supported research can be remedied by executive action, and (3) the heavy legislative schedule may preclude action in this session of Congress. In view of these developments, it seems prudent to explore the willingness of the Executive Branch to use the authority of section 361 to cover privately-funded recombinant DNA research. In addition, we request that you solicit a legal opinion from the Department of Justice as to the use of section 361 in this manner.

There is an additional factor to consider. In the past, Congress has been reluctant to extend statutory control over a specific field of scientific investigation unless such authority was absolutely necessary to protect the public's health and safety. In view of the scientific evidence accumulated during the past year, it is not possible to reach this conclusion in the case of recombinant DNA research. If the deficiencies discussed above could be corrected through executive action—by use of existing powers of FDA and/or the authority of section 361—there would be no reason to legislate new statutory controls.

In the event these executive actions were implemented, we would recommend that an appropriate group of experts and lay persons, such as the advisory committee to the NIH Director, continue to monitor the scientific evidence relating to the hypothetical risks of recombinant DNA research. If evidence indicating actual risks were to be developed, Congress could once again consider the need for legislation.

Since we are presently considering the legislative agenda for the balance of this session, we would appreciate your prompt response to this inquiry.

Sincerely,

EDWARD M. KENNEDY,  
*Chairman, Subcommittee on  
Health and Scientific  
Research.*

JACOB K. JAVITS,  
*Ranking Minority Member,  
Committee on Human Resources.*

GAYLORD NELSON,  
*Member,  
Committee on Human Resources.*

ADLAI E. STEVENSON,  
*Chairman, Subcommittee on  
Science,  
Technology and Space.*

HARRISON A. WILLIAMS, JR.,  
*Chairman,  
Committee on Human Resources.*

RICHARD S. SCHWEIKER,  
*Ranking Minority Member, Sub-  
committee on Health and Sci-  
entific Research.*

THE SECRETARY OF HEALTH,  
EDUCATION, AND WELFARE,  
Washington, D.C. September 12, 1978.  
HON. EDWARD M. KENNEDY,  
*Chairman, Subcommittee on Health and  
Scientific Research, Committee on  
Human Resources, United States Senate,  
Washington, D.C. 20510*

DEAR TED: Thank you for your letter in which you have raised a number of thoughtful questions concerning the need for legislation to regulate recombinant DNA research.

As you state in your letter, new scientific information, particularly on the safety of *E. coli* K-12 (the principal organism used in these experiments), indicates that extensive regulation in this research area may be unwarranted. Indeed, there is additional evidence that many recombinant DNA manipulations in the laboratory may be similar to events that occur in nature.

In view of these scientific developments, you raise the question as to whether legislation is necessary or whether existing statutory authority would be sufficient for purposes of regulation. You cite specifically the regulatory authority of the FDA and of the Public Health Service Act (Section 361).

The Department does not intend to invoke existing statutory authorities to regulate DNA activities at this time. If an emergency were to occur before passage of legislation, the Department could reconsider this position in order to take action on an interim basis. But, we continue to support legislation if it embodies the moderate approach of H.R. 11192. The virtue of such legislation is that it may include a number of specific provisions that permit useful flexibility in implementing regulations. Such provisions include:

- the promotion of uniform national standards,
- clear authority for the Secretary in relationship to other Federal laws,
- avoidance of normal administrative procedures for initial application of NIH Guidelines and waiver of the Administrative Procedures Act (APA) for issuance of administrative regulations, and authority for the Secretary to waive regulatory requirements for activities that pose no significant risk to health or the environment.

In recommending legislation, the Federal Interagency Committee on Recombinant DNA Research reviewed all existing statutory authority and found that none could provide for comprehensive regulation of these activities. The Interagency Committee noted that under Section 361 "there would presumably have to be a reasonable basis for concluding that the products of all re-

## NOTICES

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combinant DNA research cause or may cause human disease. Such a conclusion would undoubtedly be tenuous at best, and it is unlikely that resulting requirements could be effectively imposed and enforced."

Your letter suggested that we seek a legal opinion from the Department of Justice on the use of Section 361. Justice is represented in the Interagency Committee and has participated in the review and recommendations concerning existing statutory authorities, including Section 361.

The authorities of the Food and Drug Administration (FDA) were reviewed by the Committee; but inasmuch as recombinant DNA research has not yet reached the stage where it has yielded products to be regulated by FDA, it was agreed that FDA probably does not have authority to impose requirements on such research at present.

On July 28, the Department published proposed revisions to the Guidelines on recombinant DNA research for 60 days of comment. In addition, I have asked General Counsel Peter Libassi to serve as Chairman and Dr. Donald Fredrickson as Vice Chairman of a September 15 public hearing on these proposed revisions. Analysis of written and oral comments will proceed as quickly as possible, with final issuance of the revised Guidelines expected before the first of December.

A number of proposed changes in the Guidelines would permit, on a voluntary

basis, registration of activities and NIH certification of new host-vector systems from the private sector. Protection would be provided for proprietary patent information for these private sector activities. Registration of recombinant DNA projects, irrespective of source of funding, would be required of institutions receiving NIH support for recombinant DNA research. By these means, a national registry of all Federal and private sector activities may evolve.

The Interagency Committee has been an invaluable forum for developing coherent and coordinated policies through the representation of all the relevant research and regulatory agencies, and has served to ensure a commonality of standards. This Committee should continue to provide such oversight for the development of Federal policies and to ensure institutional compliance with the NIH Guidelines. Other advisory committees, both technical and public, must continue. The Recombinant DNA Advisory Committee will have a continuing role, and as you suggest in your letter, the public Advisory Committee to the Director, NIH, should continue to consider recommendations from the technical group.

The NIH and the Center for Disease Control (CDC) will continue to work closely as they have done over the past 18 months concerning safety aspects of the Guidelines. For example, NIH, in conjunction with CDC, has been developing mechanisms for assisting institutions in managing possible

laboratory emergencies and for providing direct assistance when appropriate. Indeed, NIH and CDC are collaborating in a revision of the CDC Classification of Etiologic Agents on the Basis of Hazards—a classification that underpins some of the safety requirements of the Guidelines. Also, these agencies are reviewing packaging and shipping requirements relevant to recombinant DNA activities.

Close cooperation and consultation with the Food and Drug Administration and the Environmental Protection Agency will also be essential, since the regulatory authority of these agencies will come into play when recombinant DNA research inventions are ready for commercial development. The Occupational Safety and Health Administration will exercise its regulatory authority in the workplace.

We are pleased with the progress made in the absence of legislation and believe that invocation of existing authorities, however appropriate, would not contribute materially to our objectives. Only passage of legislation embodying the features cited here would, in our opinion, justify the change from a voluntary to a regulatory approach. Should the Senate choose to act, I would strongly urge adoption of an approach similar to H.R. 11192.

Sincerely,

JOSEPH A. CALIFANO, Jr.

[FR Doc. 78-35532 Filed 12-21-78; 8:45 am]



















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